K040887

510(K) SUMMARY OF SAFETY AND EFFECTIVENESS

General Information

Submitted by: B·R·A·H·M·S Aktiengesellschaft
Neuendorfstrasse 25
D-16761 Hennigsdorf near Berlin
Germany

Phone: +49 (0) 3302/883 0
Fax: +49 (0) 3302/883 100

Contact Person: Jonas Leichtner
B·R·A·H·M·S Diagnostica, LLC
6353 Genoa Road
Tracys Landing, MD 20779 USA

Phone: (410) 286 0067
Fax: (410) 286 0068
Email: j.leichtner@brahms.de

Date Prepared: December 22, 2004

Device Name

Trade Name: B·R·A·H·M·S PCT LIA
Common Name: Endotoxin Activity Assay
Classification Name: Assay, Endotoxin Activity, Chemiluminescent

Predicate Device

Manufacturer	Product Name	510(k) No.
Spectral Diagnostics, Inc.	Endotoxin Activity Assay (Eaa) Device	K021885

Device Description

B·R·A·H·M·S PCT LIA is an immunoluminometric assay (ILMA) used to determine the concentration of Procalcitonin (PCT) in human serum and plasma. Two antigen-specific monoclonal antibodies that bind PCT (the antigen) at two different binding sites (the calcitonin and katacalcin segments) are added in excess. One of these antibodies is luminescence labeled (the tracer), and the other is fixed to the inner walls of the tube (coated tube system).

During the course of incubation, both antibodies react with PCT molecules in the sample to form "sandwich complexes". As result the luminescence labeled antibody is bound to the inner surface of the tube. Once the reaction is completed, the excess tracer is completely removed from the tube and discarded.

Then, the amount of residual tracer on the test tube wall is quantified by measuring the luminescence signal using a suitable luminometer and the B·R·A·H·M·S Basiskit LIA reagents. The intensity of the luminescence signal (RLU) is directly proportional to the PCT concentration in the sample. After a standard curve has been established using standards with known antigen concentrations (calibrated against recombinant intact human PCT), the unknown PCT concentrations in patient serum or plasma samples can then be quantitated by comparison of test values with the curve.

The contents of the B·R·A·H·M·S PCT LIA kit are:

Reagent	*Quantity for 100 det.*	*Contents*
A	1 vial lyophilized	Tracer, luminescence labeled (acridinium derivate) anti-PCT antibody (monoclonal, mouse), blue colored solution, 29 ml after reconstitution with buffer B.
B	1 x 29 ml vial	Buffer, for reconstituting tracer A, ready for use.
C	2 x 50 tubes	Coated tubes (test tubes), coated with anti-PCT antibody (monoclonal, mouse), ready for use.
G	1 x 4 ml vial	Zero serum (human serum), for reconstituting the standards resp. calibrators and controls, ready for use.
W	2 x 11 ml vials	B·R·A·H·M·S Washing solution universal, concentrate, 11ml.
S1, S2/C1, S3, S4/C2, S5, S6	6 vials lyophilized	PCT standards (recombinant), reconstitute each with 0.25 ml zero serum G before use. Concentration ranges: 0.08 (def.); 0.3 – 0.7; 1.5 – 2.5; 16 – 24; 160 – 240; 400 – 600 ng/ml. Precise concentrations see leaflet enclosed.
K1, K2	2 vials lyophilized	PCT controls 1 and 2, reconstitute each with 0.25 ml zero serum G before use. Concentrations see leaflet enclosed.

Intended Use

The B·R·A·H·M·S PCT LIA is an immunoluminometric assay (ILMA) used to determine the concentration of PCT (procalcitonin) in human serum and plasma.

The B·R·A·H·M·S PCT LIA is intended for use in conjunction with other laboratory findings and clinical assessments to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock.

Technological Comparison

The B·R·A·H·M·S PCT LIA immunoassay kit is similar to the Spectral Diagnostics Endotoxin Activity Assay (K021885) in the indications for use regarding risk assessment of patients for progression to severe sepsis in conjunction with other clinical information. The B·R·A·H·M·S PCT LIA test differs from the Spectral Diagnostics Endotoxin Activity Assay in assay principle, using solid phase, in performance and result in the B·R·A·H·M·S PCT LIA assay, two antigen-specific monoclonal antibodies bind PCT (the antigen) at two different binding sites (the calcitonin and katacalcin segments). The intensity of the luminescence signal (RLU) is directly proportional to the PCT concentration in the sample. The Spectral Diagnostics Endotoxin Activity Assay measures the endotoxin activity in whole blood by the priming of host neutrophil respiratory burst activity via complement opsonized LPS-IgM immune complexes. The luminol reaction in the presence of immune complexes emits light energy. This light energy is measured and recorded by a luminometer. The Relative Light Units (RLU) measured by the instrument are converted by calculation into an Endotoxin Activity (EA) value which is reported as a percentage proportion of the total possible activity (0-1.0).

Performance Summary

Precision and Reproducibility

Based on NCCLS testing, the analytical sensitivity was determined to be 0.1 ng/ml and the functional assay sensitivity (FAS) was determined to be 0.3 ng/ml. In addition, the total precision ranges from 5.3 – 16.6 % CV and the within run precision ranges from 2.4 – 10 % CV.

High Dose Hook Effect

A High Dose Hook Effect occurs in immunometrical assay systems and yields erroneously low PCT results in cases of very high PCT concentrations (beyond 900 ng/ml after calibration).

Therefore, if a PCT result above the highest standard is obtained, the samples should be diluted with the dilution serum (Zero serum) contained in the assay kit and the test should be re-run in order to obtain the correct PCT concentration. PCT concentrations up to 4000 ng/ml do not have an effect on the assignment of the patient to the reference ranges described above.

Interference and Cross Reactivity

Based on NCCLS testing, the following substances were evaluated in the B·R·A·H·M·S PCT LIA at the concentrations listed and were found not to affect test performance.

Interfering Substance	Non-Interfering Concentration
Bilirubin (conjugated)	40 mg/dl
Triglyceride	634 mg/dl
Hemoglobin	500 mg/dl
Protein (Albumin)	1 g/dl
Imipenem	1.18 mg/ml
Cefotaxim	90 mg/dl
Vancomycin	3.5 mg/ml
Dopamine	13 mg/dl
Noradrenaline	2 µg/ml
Dobutamine	11.2 µg/ml
Heparin	8000 U/l
Furosemide	2 mg/dl
Calcitonin	8 ng/ml
Katacalcin	30 ng/ml
a-CGRP*	30 ng/ml
ß-CGRP*	30 ng/ml
Calcitonin Salmon	30 µg/ml
Calcitonin Eel	30 µg/ml

*Calcitonin Gene Related Peptide

Method Comparison Summary

The clinical data for the B·R·A·H·M·S PCT LIA were obtained in two independent, controlled prospective studies performed in the ICUs of academic hospital settings

The data from the two studies is summarized in the following graph and tables. The 2x2 tables below show the PCT results for SIRS and Sepsis compared to Severe Sepsis and Septic Shock on the first day of ICU admission.

Study 1: Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit
Müller B. et al., Crit. Care Med. 2000; 28(4): 977-983.

Patients: 101 consecutive critically ill patients of representative population of unselected, well-defined patients in a medical ICU in the Switzerland. The median age of the study population was 59 years (age range, 23-86 years). There were 55 men and 46 women in this study.

Study 2: Diagnostic Value of Procalcitonin, Interleukin-6 and Interleukin-8 in Critically Ill Patients admitted with suspected Sepsis
Harbarth S. et al., Am. J. Resp. Crit. Care Med. 2001; 164: 396-402.

Patients: 78 consecutive critically ill patients newly admitted to a medical and surgical ICU in the Switzerland, including also neutropenic and immunosuppressed patients, with suspected diagnosis of infection. Patients had to fulfill at least 2 criteria of SIRS. Source of infection was the respiratory tract, intra-abdominal space and bloodstream infection. The mean ages were as follows: SIRS, 51 ± 18 years; sepsis, 51 ± 21 years; severe sepsis, 59 ± 18 years; and septic shock, 54 ± 15 years. There were 57 men and 21 women in this study.

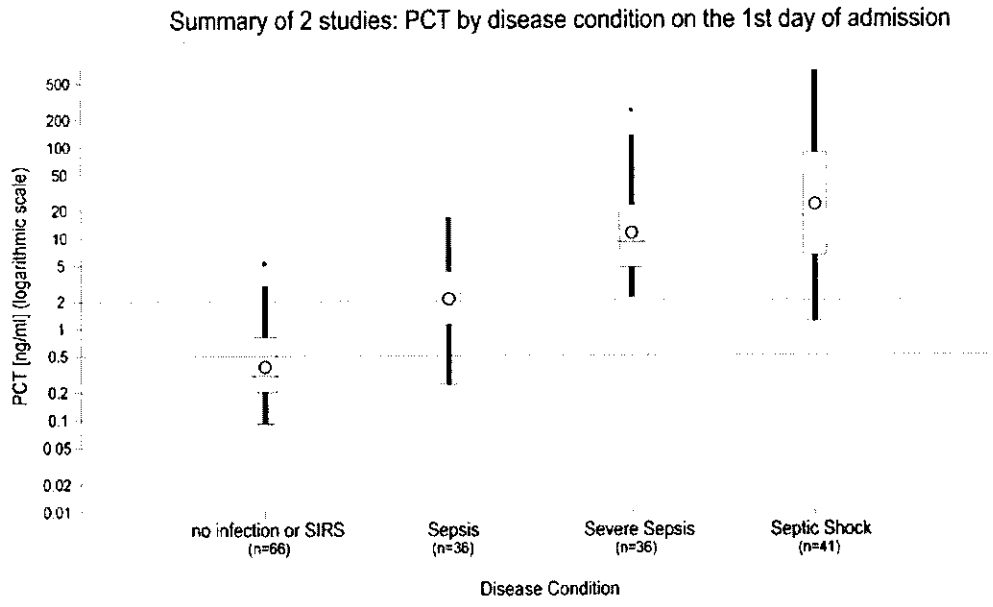
PCT by no infection or SIRS, Sepsis versus Severe Sepsis or Septic Shock Cut Off 0.5 ng/ml

PCT Result Study 1	No infection or SIRS/Sepsis	Severe Shock/ Septic Shock	Totals
PCT < 0.5	36	0	36
PCT > 0.5	34	31	65
Totals	70	31	101
PCT Result Study 2	SIRS/Sepsis	Severe Shock/ Septic Shock	Totals
PCT < 0.5	8	0	8
PCT > 0.5	24	46	70
Totals	32	46	78

PCT by no infection or SIRS, Sepsis versus Severe Sepsis or Septic Shock
Cut Off 2.0 ng/ml

PCT Result Study 1	No infection or SIRS/Sepsis	Severe Shock/ Septic Shock	Totals
PCT < 2.0	60	0	60
PCT > 2.0	10	31	41
Totals	70	31	101
PCT Result Study 2	SIRS/Sepsis	Severe Shock/ Septic Shock	Totals
PCT < 2.0	19	1	20
PCT > 2.0	13	45	58
Totals	32	46	78

The 4 box and whisker diagrams below summarize the individual PCT results of the 4 subgroups of patients on the first day of ICU admission.



Interpretation of Results

The data from the two studies supports the following interpretative risk assessment criteria:

PCT > 2 ng/ml

PCT levels above 2.0 ng/ml on the first day of ICU admission represent a high risk for progression to severe sepsis and/or septic shock.

PCT < 0.5 ng/ml

PCT levels below 0.5 ng/ml on the first day of ICU admission represent a low risk for progression to severe sepsis and/or septic shock.

PCT levels below 0.5 ng/ml do not exclude an infection, because localized infections (without systemic signs) may also be associated with such low levels. If the PCT measurement is done very early after the systemic infection process has started (usually < 6 hours), these values may still be low.

As various non-infectious conditions are known to induce PCT as well, PCT levels between 0.5 ng/ml and 2.0 ng/ml should be reviewed carefully to take into account the specific clinical background and condition(s) of the individual patient.

Expected Values

In normal subjects, PCT concentrations are < 0.3 ng/ml, thus below the detection limit of the assay. In a population of 144 healthy subjects 143 had a PCT value < 0.3 ng/ml.

Specimen Collection and Handling

Serum or plasma may be used for the B·R·A·H·M·S PCT LIA. However, only one matrix, i.e., the same material (either serum or plasma), should be used throughout the patient's clinical course.

NCCLS guidelines should be followed for collecting, transporting, and processing patient samples. A slight difference in results was noted between the use of glass and plastic collecting tubes. For plastic tubes, a slight increase is noted if the sample remains in the collecting tube for more than 24 hours, if the filling volume is higher, or if plasma is used. B·R·A·H·M·S recommends the use of one type of collecting tube, i.e., either glass or plastic, throughout the patient's clinical course.

Samples that are not used in an assay within 24 hours following the blood draw must be frozen and stored at –20 °C. Samples may be frozen and thawed three times.

Conclusions

The B·R·A·H·M·S PCT LIA is substantially equivalent to the legally marketed Endotoxin Activity Assays in intended use.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

JAN - 7 2005

Mr. Jonas Leichtner
Project Manager
B.R.A.H.M.S Diagnostica, LLC
6353 Genoa Road
Tracys Landing, MD 20779

Re: k040887
Trade/Device Name: B.R.A.H.M.S PCT LIA
Regulation Number: 21 CFR 866.3610
Regulation Name: Endotoxin Assay
Regulatory Class: Class II
Product Code: NTM
Dated: December 1, 2004
Received: December 1, 2004

Dear Mr. Leichtner:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and 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) that do not require approval of a premarket approval application (PMA). 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 (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820).

This letter will allow you to begin marketing your device as described in your Section 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 information about the application of labeling requirements to your device, or questions on the promotion and advertising of your device, please contact the Office of *In Vitro* Diagnostic Device Evaluation and Safety at (240)276-0484. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html

Sincerely yours,

Sally A. Hojvat, M.Sc., Ph.D.
Director
Division of Microbiology Devices
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and
Radiological Health

Enclosure

INDICATIONS FOR USE

510(k) Number (if known): K040887

Device Name: B·R·A·H·M·S PCT LIA

Sponsor Name: B·R·A·H·M·S Aktiengesellschaft

Indications for Use:

The B·R·A·H·M·S PCT LIA is an immunoluminometric assay (ILMA) used to determine the concentration of PCT (procalcitonin) in human serum and plasma.

The B·R·A·H·M·S PCT LIA is intended for use in conjunction with other laboratory findings and clinical assessments to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock.

Prescription Use ☒ (21 CFR 801 Subpart D) And/Or Over-The-Counter Use ☐ (21 CFR 807 Subpart C)

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Concurrence of CDRH, Office of Device Evaluation (ODE)

Division Sign-Off

Office of In Vitro Diagnostic Device Evaluation and Safety

510(k) K040887