K030655

JAN 2 9 2004

510(K) Summary
Axis-Shield HoloTC RIA

Summary of Safety and Effectiveness Information Supporting a Substantially Equivalent Determination

Statement of Intended Use

The Axis-Shield HoloTC RIA is an in-vitro diagnostic assay for quantitative measurement of holotranscobalamin (vitamin B_{12} bound to transcobalamin) in human serum or plasma. Measurements obtained by this device are used in the diagnosis and treatment of vitamin B_{12} deficiency. HoloTC RIA is calibrated with HoloTC Calibrators. HoloTC controls are assayed for the verification of the accuracy and precision of the HoloTC RIA.

Summary of Technological Characteristics

The Axis-Shield HoloTC RIA is a competitive binding immunoassay in which a specific monoclonal antibody is used to capture transcobalamin from the patient sample. Thereafter the procedure is as commonly used in vitamin B12 assays. The cobalamin (vitamin B12) is released from the transcobalamin using dithiothreitol and sodium hydroxide. The released cobalamin (vitamin B12) then competes for a limited amount of intrinsic factor with added ^{57}Co labelled vitamin B12. The Axis-Shield HoloTC RIA differs from the predicate device in two main aspects:

1) The use of a transcobalamin specific antibody, this allows the quantitation of only the cobalamin bound to the protein transcobalamin as opposed to measurement of cobalamin bound to all proteins in the predicate device and
2) The detection signal is radioactivity (^{57}Co) as opposed to chemiluminescence in the predicate device.

Method Comparison

The Axis-Shield HoloTC RIA was compared to the Bayer Advia Centaur VB12 assay (K993571) using 392 patient samples with vitamin B12 concentrations ranging from 114-821 pmol/L.

Linear regression (least squares) yielded the following statistics:

$\sqrt{}$HoloTC pmol/L = 0.55$\sqrt{}$VB12-2 pmol/L

$r^2 = 0.52$

Reference Interval

Based on a Finnish population of normal individuals (n=303, age 22-88 years) the 95% central reference interval was found to be 37-171 pmol/L.

Analysis of covariance demonstrated that HoloTC levels depended on gender (but not age) in this reference population. The 90 % confidence intervals for the lower limit of the reference range are for the whole population, males and females 36-37 pmol/L, 37-39 pmol/L and 35-36 pmol/L, respectively.

External Evaluation

The Axis-Shield HoloTC RIA external laboratory performance was evaluated at two external study sites, UK and Denmark. Performance of the system was demonstrated by using three different levels of native and pooled serum samples in addition to kit controls Low and High. CV for the three serum samples were within the given acceptance criteria, <15 %.

Precision

Precision studies were done according to NCCLS standard. Precision of the system was demonstrated by using three levels of serum samples, low, medium and high (14, 67 and 139 pmol/L HoloTC, respectively). Within-run CV for duplicate measurements of serum low, medium and high were 11%, 5% and 8%, respectively and total precision was 11%, 6% and 8%, respectively.

Linearity

Dilution Linearity within the working range of 10-160 pmol/L was demonstrated to meet all criteria for linearity. Recovery test of HoloTC spiked serum samples was demonstrated to be within acceptance criteria. Dilution of high HoloTC sample into six dilutions showed a correlation coefficient $r^2 = 0.998$, slope = 1.01 ± 0.02 and y-intercept = -5 ± 2 pmol/L for dilutions ranging between 13 - 182 pmol/L HoloTC. Limit of Quantification (LOQ) and Limit of Detection (LOD) were demonstrated to be 8-176 pmol/L and 6 pmol/L, respectively. Cross-reactivity was tested against haptocorrin (HC) and cross-reactivity was well within the acceptance criteria of ±10% for up to 70,000pg/mL HC spiked serum samples.

Interference

Effect on quantification by endogenous interfering substances was tested. bilirubin, haemoglobin, total protein and lipids showed less that 10% interference.

Serum/EDTA Plasma comparison

50 paired serum and EDTA plasma samples collected from the same donors were analysed and compared. No significant difference in measured HoloTC level was demonstrated between serum sample and EDTA sample. In-use stability of the reagent and calibrator kit showed stability up to three months after opening.

Sensitivity and Specificity

The estimated concordance and relative sensitivity and specificity of HoloTC RIA was calculated using samples from 3 study sites that were classified as being likely (n=112) and not likely (n=313) vitamin B12 deficient based on cobalamin and MMA levels. A general parametric approach was used. The estimated concordance, sensitivity, and specificity for each study was weighted and then all were combined to give the following estimates; concordance 80%, sensitivity 99.5%, specificity 76.3%.

Conclusion

In conclusion these data demonstrate that the Axis-Shield HoloTC RIA is as safe and effective as, and is substantially equivalent to, the Bayer Advia Centaur VB12 assay.

Contact information:

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
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JAN 2 9 2004

Axis-Shield Biochemicals, ASA
c/o Ronald G. Leonardi, Ph. D.
President
R & R Registrations
P.O. Box 262069
San Diego, CA 92196-2069

Re: k030655
Trade/Device Name: Axis-Shield Holo TC RIA
Regulation Number: 21 CFR 862.1810
Regulation Name: Vitamin B_{12} test system
Regulatory Class: Class II
Product Code: CDD; JIS; JJX
Dated: November 4, 2003
Received: November 5, 2003

Dear Dr. Leonardi:

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 (301) 594-3084. 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/dsma/dsmamain.html.

Sincerely yours,

Jean M. Cooper MS, DVM.

Jean M. Cooper, MS, D.V.M.
Director
Division of Chemistry and Toxicology
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and
Radiological Health

Enclosure

510(k) Number (if known) K030655

Device Name:Axis-Shield HoloTC RIA

INDICATIONS FOR USE:

The Axis-Shield HoloTC RIA is an in-vitro diagnostic assay for quantitative measurement of the fraction of cobalamin (vitamin B_{12}) bound to the carrier protein transcobalamin in human serum or plasma. Measurements obtained by this device are used in the diagnosis and treatment of vitamin B_{12} deficiency.

(PLEASE DO NO WRITE BELOW THIS LINE – CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use ✓ **OR** **Over-The-Counter Use** ___
(Per 21 CFR 801.109)

(Optional Format 1-2-96)

Carol C Benson for Jean Cooper, DHHM

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K030655