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510(k) Summary of Safety and Effectiveness

Ventana Medical Systems, Inc. developed the Ventana Leukocyte Common Antigen Primary Antibody for use on the Ventana ES automated immunohistochemistry system. Ventana Leukocyte Common Antigen Primary Antibody (clone RP2/18) is substantially equivalent to a commercially available leukocyte common antigen (clones 2B11 and PD7/26).

Leukocyte Common Antigen (LCA) is a family of five to eight glycoproteins (MW 180 to 220 kd) encoded on chromosome 1q32¹. Leukocyte Common Antigen or CD45 proteins are found on all cells of hematopoietic origin, except erythrocytes. LCA has phosphatase activity and appears to activate tyrosine protein kinase¹. Various isoforms are generated by alternative splicing of three exons that can be inserted after an NH₂-terminal sequence of eight amino acids found on all isoforms². The various isoforms are expressed differently on different lymphoid cells and are distinguished by epitopes termed CD45RA, CD45RB, CD45RC and CD45RO². Ventana Medical Systems' Leukocyte Common Antigen Primary Antibody (Clone RP2/18) contains a mouse monoclonal antibody directed against the CD45RB epitope found on the membrane of leukocytic cells^{3,4}. The Clone RP2/18 has been shown to react with the 220-, 205-, 190 kD isoforms of CD45^{3,4}. Clone RP2/18 has not been classified by the Workshop on Human Leucocyte Differentiation Antigens, and therefore, has no CD designation.

Clinical Significance

Early studies showed the utility of LCA antibody in distinguishing hematopoietic neoplasms, particularly of lymphoid type, from poorly differentiated tumors of epithelial, mesenchymal or neural derivation⁵. Warnke et.al.⁶ showed the utility of LCA antibody in routinely processed, paraffin-embedded tissue revealing high specificity and sensitivity for non-Hodgkin's lymphoma. The greatest utility of LCA antibody is in the characterization of a neoplasm in which the differential diagnosis includes a non-hematolymphoid neoplasm⁷. The histologic appearance of anaplastic large cell lymphoma with large anaplastic cells in sheets, clusters, or invading sinuses may mimic metastatic carcinoma or melanoma¹. The antibody has been nonreactive with most carcinomas and tissues of epithelial and neural origin, as well as malignant melanomas, rhabdomyosarcomas and Ewing's sarcoma^{5,6}. However, some authorities report lack of reactivity for LCA in 10 to 30% of large cell lymphomas. For this reason a panel of antibodies employed to screen anaplastic tumors should include L26 and one or more of UCHL1 (CD45RO) and Leu 22 or MT1 (CD43), based on the rationale that these latter reagents will detect at least some of the lymphomas missed by the anti-LCA antibody^{8,9}. Furthermore, problems in interpretation can occur when assessing metastatic carcinomas in the lymph node that are scattered as individual cells. The LCA-positive lymphocytes closely apposed to carcinoma cells give the appearance of membrane reactivity to the latter cells. Clone RP2/18 shows staining is more intense in lymphoid cells on the cell surface membrane, with lesser cytoplasmic staining. Among neoplastic diseases of non-lymphocytic leukocytic origin, (monocytic, myeloid, and histiocytic neoplasms) staining is less frequent, less sensitive and more variable involving both a membranous and cytoplasmic pattern.

Comparative Study

Supporting data for the equivalence statement is shown by the following study. Formalin fixed, paraffin embedded preparations from pathologic samples were tested using Ventana Leukocyte Common Antigen Primary Antibody and a commercially available leukocyte common antigen. Normal samples were tested with Ventana product only. Samples were obtained from excess tissues obtained for reasons other than the present study. Pathologic and normal tissues were evaluated on a blinded basis for specific staining pattern and background staining by a qualified pathologist. Normal tissues such as adrenal, breast, cerebellum, cerebrum, cervix, colon, endometrium, esophagus, heart, kidney, liver, lung, mesothelium, ovary, pancreas, peripheral nerve, pituitary, prostate, salivary gland, skeletal muscle, skin, small intestine, stomach, testis, thyroid, were evaluated. Slides were processed on the Ventana ES Automated Slide Stainer and prepared for examination.

Results

When compared with a commercially available leukocyte common antigen antibody, Ventana Leukocyte Common Antigen Primary Antibody stained the same tissues 100% of the time in lymphocytic line cancers. Neither Ventana Leukocyte Common Antigen Primary Antibody nor the commercially available antibody stained any of the non-lymphocytic type cancers. The staining patterns of the normal tissues were considered to be appropriate.

Staining in normal lymph node and tonsil was found in both B cell regions (germinal centers, mantle zones) and paracortical T cell zones in a membranous pattern. While lesser, variable membranous and sometimes cytoplasmic staining was found in histiocytes and granulocytes and staining was absent in blood vessels, connective tissue and plasma cells.

In bone marrow and spleen, scattered lymphoid cells with membranous staining contrast with weak staining in histiocytes and macrophages which is variably membranous and cytoplasmic. Polymorphonuclear granulocytes are usually negative but occasionally weakly reactive with variable membranous and cytoplasmic staining pattern.

In other normal tissues such as adrenal, breast, cerebellum, cerebrum, cervix, colon, endometrium, esophagus, heart, kidney, liver, lung, mesothelium, ovary, pancreas, peripheral nerve, pituitary, prostate, salivary gland, skeletal muscle, skin, small intestine, stomach, testis, thyroid, no specific staining of cells occurred.

Clone RP2/18 shows staining is more intense in lymphoid cells on the cell surface membrane, with lesser cytoplasmic staining. Staining is most consistent for lymphocytic cells with less consistent reaction in other leukocytes (macrophages/histiocytes/myeloid cells). The antibody generally labels neoplastic B cells and T cells in non-Hodgkin's Lymphomas within all Working Formulation categories (A-J). The neoplastic cells of Hodgkin's lymphomas (Reed-Sternberg and Lacunar cells, show no membranous reactivity in the majority of cases, although closely approximated reactive lymphoid cells make interpretation difficult. Rare non-specific cytoplasmic staining in Reed-Sternberg cells and Lacunar cells was observed. Among the myeloid and monocytic leukemias a minority showed membranous reactivity in the neoplastic

cells. Among non-hematopoietic neoplasms, breast, colon, oat cell, and ovarian carcinomas, there was no staining by anti-LCA (clone RP2/18). Specificity of both antibodies was proven with appropriate staining of cells of leukocytic lineage and no staining of cells of non-leukocytic lineage. Sensitivity of Leukocyte Common antigen antibodies, based on comparison of 20 lymphocytic cancers, showed that Ventana Leukocyte Common Antigen Primary Antibody stained 17 of 20 and the commercially available leukocyte common antigen stained 17 of 20.

Staining intensity was scored on a scale of 0 - 4+. Non parametric analysis of the staining intensity results from pathologic tissue (Wilcoxon matched pairs) shows no difference in the performance of the two antibodies tested, at the .01 level of significance.

Intra-run reproducibility, based on 10 samples of the same tissue within one run, were similar for both antibodies. Inter-run reproducibility, based on samples of the same tissue on 10 different instrument runs, showed similar staining.

References

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3. Zapata JM, Pulido R, Acevedo A, Sanchez-Madrid F and de Landazuri MO. Human CD45RC Specificity. *J Immunol.* 1994;152:3852-3861.
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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OCT 20 1997

Re: K940583/S3
Trade Name: Ventana Medical Systems, Inc. Leukocyte
Common Antigen Primary Antibody
(clone RP2/18)
Regulatory Class: II
Product Code: DEH
Dated: July 25, 1997
Received: July 25, 1997

Dear Dr. Tillson:

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 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 (Pre-market 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 Good Manufacturing Practice for Medical Devices: General (GMP) regulation (21 CFR Part 820) and that, through periodic GMP 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 pre-market 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.

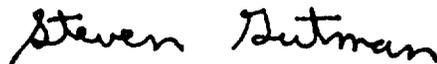
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Under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88), this device may require a CLIA complexity categorization. To determine if it does, you should contact the Centers for Disease Control and Prevention (CDC) at (770) 488-7655.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification immediately.

An FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and permits your device to proceed to the market, but it does not mean that FDA approves your device. Therefore, you may not promote or in any way represent your device or its labeling as being approved by FDA. 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), promotion, or advertising please contact the Office of Compliance, Promotion and Advertising Policy Staff (HFZ-302) at (301) 594-4639. 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.

Sincerely yours,



Steven I. Gutman, M.D., M.B.A.
Director
Division of Clinical
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