K965022

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510(k) Summary

Submitter: DAKO Corporation
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Contact: Gretchen M. Murray, Ph.D., RAC Regulatory Affairs Asst. Manager

Date Summary Prepared: July 28, 1997

Device name:
1) Monoclonal Mouse Anti-Human Ki-1 antigen, CD30, Clone Ber-H2 (Product Code No. M0751)

2) Ready-To-Use Monoclonal Mouse Anti-Human Ki-1 antigen, CD30, Clone Ber-H2 and Negative Control Reagent (Product Code No. N1558)

Primary Antibody Device Classification: Class I or Class II has been proposed for immunohistochemical staining reagents.

Panel: The proposed device classification is under the Hematology and Pathology devices panel, Division of Clinical Laboratory Devices.

Predicate Device: DAKO Monoclonal Mouse Anti-Human LCA (Product Code No. M0701, FDA K896918/B)

Device Description:
1) Monoclonal Mouse Anti-Human Ki-1 antigen, CD30, Clone Ber-H2 (Product Code No. M0751) is a mouse anti-human monoclonal antibody produced as a tissue culture supernatant. The antibody is supplied in 0.05M Tris-HCl buffer, pH 7.2, containing 0.015M sodium azide. (1 ml total volume)

2) Ready To Use Monoclonal Mouse Anti-Human Ki-1 antigen, CD30, Clone Ber-H2 Primary Antibody and Negative Control Reagent (Product Code No. N1558) consists of a mouse anti-human monoclonal antibody produced as a tissue culture supernatant and pre-diluted in 0.05M Tris-HCl buffer, pH 7.6, containing carrier protein and 0.015M sodium azide (7mL total volume). The primary antibody is packaged with a negative control reagent consisting of fetal calf serum in 0.05M Tris-HCl buffer, pH 7.6, containing carrier protein and 0.015M sodium azide (5 ml total volume). The primary antibody and the negative control reagent contain equivalent total protein concentrations.

Intended Use: For *In Vitro* Diagnostic Use

Monoclonal mouse anti-human Ki-1 antigen, CD30, clone Ber-H2, is intended for laboratory use to qualitatively identify by light microscopy the lymphocyte activation-associated antigen designated CD30 in acetone fixed, frozen and formalin or B5 fixed, paraffin-embedded tissues. Ber-H2 specifically binds to antigens located on the cell membrane, as well as in the Golgi region of activated lymphoid cells. Positive results aid in the classification of normal and abnormal cells and tissues and serve as an adjunct to conventional histopathology.

ıdicated Use: Monoclonal mouse anti-human Ki-1 antigen, CD30, Clone Ber-H2, may be used as one member of a panel of antibodies to aid in the differential diagnosis of large anaplastic cells of undetermined origin. This antibody stains cell membranes of most cases of anaplastic large cell lymphomas (ALCL), often called Ki-1 lymphomas. It also stains cell membranes and/or cytoplasm of most Hodgkin's lymphomas. Ber-H2 is a valuable aid in the assessment of cutaneous lymphoid infiltrates, particularly when large atypical cells are

present. Most nonhematolymphoid neoplasms are negative with Ber-H2, although there are several significant exceptions.

The staining pattern is most often described as strong membranous and weaker cytoplasmic, specifically paranuclear dot-positivity of the Golgi region. Membrane positivity is seen with embryonal carcinomas, and weak, diffuse cytoplasmic positivity is seen in pancreatic and salivary gland carcinomas.[3] The weak, diffuse cytoplasmic staining is considered to be unexpected, non-specific labeling. It may be reduced or removed by changing the protease pretreatment of the paraffin sections and/or further dilution of the Ber-H2 antibody.[3]

The clinical interpretation of any positive staining or its absence should be complemented by morphological and histological studies with proper controls. Evaluations should be made within the context of the patient's clinical history and other diagnostic tests by a qualified individual having knowledge of all the potential antibody reactivities.

Experimental Data

Normal Tissue Testing:

The required panel of normal tissues was tested with this antibody as specified in the 3/28/95 draft of *Guidance for Submissions of Immunohistochemistry Applications to the FDA*. Additionally tested were three specimens of spinal cord. All tissues were formalin fixed and paraffin embedded. Staining was performed using the DAKO LSAB®2 Peroxidase (Code No. K0677) and LSAB®2 Alkaline Phosphatase (Code No. K0676) kit systems.

Normal tissues exhibiting positive staining with Ber-H2 included the following: a subpopulation of myelocytes in bone marrow, brain (Purkinje cells in cerebellum and ganglion cells in cerebrum), motor neurons and axons in spinal cord, and peri/interfollicular lymphocytes in tonsil. The other tissues were negative for specific staining.

Reproducibility Testing:

Eight serial sections from each of three different paraffin embedded blocks of Hodgkin's Lymphoma (pre-screened for low antigen density) were collected for testing. Testing was performed as follows:

Intra-run reproducibility: Following the standard DAKO LSAB®2 Peroxidase Kit protocol (Code No. K0677), three slides from each tissue block were stained with Ready-To-Use DAKO® Monoclonal mouse anti-human Ki-1 antigen, CD30, Clone Ber-H2 (Code No. N1558). Concurrently, one slide from each block was stained with the supplied negative control reagent.

Inter-run reproducibility: Staining one slide from each tissue block, the above procedure was repeated on two additional days. Concurrently, one slide from each block was stained with the supplied negative control reagent.

Reproducibility experiments with Ber-H2 yielded consistent results with intra- and inter-run testing. Consistent test conditions were maintained throughout the study and reagents were stored at 2-8°C between test runs.

Published Immunoreactivity

Clone Ber-H2 Characteristics

Monoclonal mouse anti-human Ki-1 antigen, CD30, Clone Ber-H2 (Ber-H2) has been shown to react with a cell membrane associated glycoprotein with an apparent molecular mass of 105 to 120 kD.[1-5] The extracellular domain of the CD30 antigen has significant homology to that of members of the tumor necrosis factor(TNF)/nerve growth factor (NGF) receptor superfamily.[5,6] This evidence suggest that CD30 antigen acts as a receptor whose ligand is a cytokine.[5] It is hypothesized that the CD30 antigen is associated with lymphoid activation because its presence is induced on B and T lymphocytes in vitro by a number of stimuli, including viruses and lectins.[5] Positive staining with Ber-H2 is typically membranous, often with cytoplasmic, and/or dot-like staining in the Golgi region.[3-5] Ber-H2 reacts with an epitope that is retained after routine fixation for paraffin embedded tissue sections unlike Ki-1, the first CD30 antibody recognized. Ber-H2 stains both paraffin-embedded and frozen tissue sections, and demonstrates greater intensity than Ki-1 on frozen tissues. The Fourth International Workshop on Leukocyte Differentiation Antigens (Vienna, 1989) recognized Ber-H2 as an antibody directed against the lymphocyte activation-associated antigen designated CD30, also known as the Ki-1 antigen.[1,3,7]

Clone Ber-H2 Positivity in Normal Tissues

In normal tissues, Ber-H2 has been characterized as reacting with scattered large activated B and T lymphoid cells localized around and between lymph follicles and at the margin of germinal centers. Some plasma cells also exhibit diffuse cytoplasmic staining in paraffin tissues only. Positive staining of few scattered blasts in the lymphoid tissue of the intestine and in the medullary part of the thymus has also been reported.[1,3,5,8] Unexpected cytoplasmic staining of normal tissues is described as follows: In bone marrow, cytoplasmic staining has been observed in late stage erythroid and myeloid cells.[9] Diffuse cytoplasmic staining has also been observed in exocrine pancreas cells. In paraffin embedded sections only, diffuse cytoplasmic staining with Ber-H2 has been observed in a proportion of cerebral cortical neurons, and Purkinje cells of the cerebellum. Fibroblasts have been reported to stain positively in paraffin sections also.[10] The diffuse weak cytoplasmic staining is controversial for specificity with Ber-H2. Some have reported that this staining is of no diagnostic relevance.[3, 5, 6]

Resting peripheral lymphocytes, monocytes, interdigitating cells, follicular dendritic cells, and macrophages were initially reported to be non-reactive with Ber-H2,[3,5] but subsequent rare Ber-H2 staining of follicular dendritic cells has been observed.[8] Activated macrophages, including those observed in frozen tissues from granulomatous inflammation, sarcoidosis, toxoplasmosis, and cat-scratch fever as well as in paraffin embedded tissues from one case of miliary tuberculosis also demonstrated Ber-H2 positivity.[8,11-12]

Anaplastic Large Cell Lymphomas

Ber-H2 stains most cases of anaplastic large cell lymphomas (ALCL). In a summary of five series of morphologically and immunologically characterized non-Hodgkin's lymphoma (NHLs), Chang, et al,[5] reported 100% Ber-H2 positivity in 139 cases of ALCL. ALCLs may account for 3 to 8% of all NHLs.[5,13] Virtually all of the neoplastic cells display membrane staining, often accompanied by paranuclear staining. Because cell membrane staining is seen in other diseases, including all major categories of NHL except lymphoblastic lymphoma, Ber-H2 positivity is not diagnostic of ALCL.[3,5,8]

Hodgkin's Lymphoma

The CD30 epitope is expressed in Hodgkin (H) and Reed-Sternberg (RS) cells in all types of Hodgkin's Disease (HD). Ber-H2 staining is particularly useful for demonstrating Hodgkin's cells in samples with few neoplastic cells or those with heavy infiltration of

macrophages.[8] Staining is usually stronger in frozen sections than in paraffin sections.[5] Ree et al.[10] reported the following staining patterns in paraffin embedded specimens from 89 undisputed Hodgkin's disease patients: 9/89 (10%) were negative, 20/89 (22%) showed membrane staining alone or in combination with paranuclear or cytoplasmic staining and 60/89 (67%) had cytoplasmic and/or paranuclear staining without membrane staining.

The incidence of positivity depends on the type of tissue processing. In frozen and plastic sections, virtually all cases have been reported to be Ber-H2 positive.[5] In a summary of a series of ten studies with paraffin sections, only 89% of cases were positive. In addition, the percentage of Ber-H2 positive results with paraffin embedded tissue also varied among types of HD as follows: 25% (14/56) of lymphocyte predominance, 87% (297/340) of nodular sclerosis, 91% (250/274) of mixed cellularity, 86% (24/28) of lymphocyte depletion, and 75% (15/20) of unclassified cases.[5]

Cutaneous Lymphoid Infiltrates

Ber-H2 positivity is also a valuable aid in the assessment of cutaneous lymphoid infiltrates, when used with a panel of antibodies. Ralfkiaer, et al,[14] stained specimens from 115 patients with benign dermatoses, pre- or pseudo-malignant disorders, and malignant cutaneous lymphomas. They reported that in 100% of 6 cases of lymphomatoid papulosis, a peripheral T-cell lymphoma, varying numbers of scattered large polymorphic lymphoid cells consistently expressed Ber-H2. The reactivity may be seen as membranous and cytoplasmic.[6] However, other peripheral T-cell cutaneous lymphomas and 3/14 (21.4%) of cases of mycosis fungoides Sezary syndrome (labeling confined to large cells present) were positive. The lymphoid cells in all other specimens were Ber-H2 negative. While these data suggest that Ber-H2 cannot distinguish cutaneous NHL from lymphomatoid papulosis, they may aid in differentiating the latter from other types of Ber-H2 negative pre- or pseudo-malignant cutaneous infiltrates.[14]

Non-Hematolymphoid Neoplasms

Although generally not found in non-hematolymphoid neoplasms, Ber-H2 positivity has been reported in both frozen and paraffin embedded tissue in salivary gland carcinomas 2/3 (67%), embryonal carcinomas 8/10 (80%), in the embryonal component of mixed germ cell tumors 4/4 (100%) and in 4/21 (19%) cases of testicular germ cell tumors.[3,15,16] Ber-H2 positivity was also reported in one case of interdigitating cell sarcoma and in 3/4 (75%) cases of follicular dendritic cell sarcoma.[8]

In summary, because of limited specificity and sensitivity, Ber-H2 positivity alone is not diagnostic for ALCL.[17] In cases of HD, the incidence of positivity depends on the type of tissue processing. In frozen and plastic sections, virtually all cases have been reported to be Ber-H2 positive. In paraffin sections only 89% of cases were positive. Similarly, only 25% of cases of lymphocyte predominance HD stained positively in paraffin sections and staining was generally weaker and confined to the cell membrane when compared to that seen in classical HD.[5]

References

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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NOV - 6 1997

Re: K965022
Trade Name: DAKO Corporation's Monoclonal Mouse Anti-Human Ki-1 Antigen, CD30, Clone Ber-H2 (Product Code No. MO751)
Regulatory Class: II
Product Code: DEH
Dated: August 8, 1997
Received: August 11, 1997

Dear Dr. Murray:

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.

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 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): K965022

Device Name: _Monoclonal Mouse Anti-Human Ki-1 antigen, CD30, Clone Ber-H2 for Immunoenzymatic Staining (DAKO Code No. M0751)

_Monoclonal Mouse Anti-Human Ki-1 antigen, CD30, Clone Ber-H2 Ready-to-Use Antibody and Negative Control for Immunoenzymatic Staining DAKO Code No. N1558)

Indications For Use:

Monoclonal mouse anti-human Ki-1 antigen, CD30, Clone Ber-H2 (Ber-H2), may be used as one member of a panel of antibodies to aid in the differential diagnosis of large anaplastic cells of undetermined origin. This antibody stains cell membranes of most cases of anaplastic large cell lymphomas (ALCL), often called Ki-1 lymphomas. It also stains cell membranes and/or cytoplasm of most Hodgkin's lymphomas. Ber-H2 is a valuable aid in the assessment of cutaneous lymphoid infiltrates, particularly when large atypical cells are present. Most nonhematolymphoid neoplasms are negative with Ber-H2, although there are several significant exceptions. Membrane positivity is seen with embryonal carcinomas, and weak, diffuse cytoplasmic positivity is seen in pancreatic and salivary gland carcinomas.

The staining pattern is most often described as strong membranous and weaker cytoplasmic, specifically paranuclear dot-positivity of the Golgi region. The weak, diffuse cytoplasmic staining is considered to be unexpected, non-specific labeling. It may be reduced or removed by changing the protease pretreatment of the paraffin sections and/or further dilution of the Ber-H2 antibody.

(PLEASE DO NOT 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)

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

IVD Use_____
(Per 21 CFR 801.119

(Optional Format 1-2-96)