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510(k) Summary

Date: September 29, 1997

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Registration #: 2028492

Trade Name: ChemMate™ Kappa

Class II

Intended Use: FOR IN VITRO DIAGNOSTIC USE.

The ChemMate™ Kappa (rabbit polyclonal anti-human kappa light chains) is intended for laboratory use to qualitatively identify by light microscopy human kappa light chains in immunoglobulin secreting plasma cells and plasmacytoid B lymphocytes in normal and pathological paraffin embedded tissues processed in zinc formalin, neutral buffered formalin, Bouin's or B5 fixative.[11,19,20] Positive results aid in the differential diagnosis, classification and immunophenotyping of lymphomas and must be interpreted by a pathologist within the context of clinical data, gross and microscopic morphological criteria and multiple chemical and immunohistochemical stains.

This antiserum has been optimally prediluted for use with the ChemMate™ SDK605 or SDK305 Secondary Detection - Peroxidase/DAB kit. Additionally, the prediluted ChemMate™ Kappa antibody as well as the ChemMate™ SDK605 Secondary Detection - Peroxidase/DAB kit has been optimized for use with the Techmate™ for automated immunohistochemical staining.

510K SUMMARY OF SAFETY AND EFFECTIVENESS

Summary and Explanation

ChemMate™ Kappa is comprised of a rabbit polyclonal antibody to human kappa light chains. The antibody reacts with free kappa light chains as well as kappa chains in intact immunoglobulin molecules.

In a large study involving paraffin-embedded tissues as well as frozen tissues and acetone fixed cryostat sections, Picker et al. demonstrated that 24 of 31 non-malignant, lymphoid hyperplasia cases, diagnosed by histologic criteria, co-expressed both kappa and lambda light chains. Six of these cases were uninterpretable, and one was light chain restricted. Further investigation of the light chain restricted case by Southern Blot analysis showed no clonal rearrangement of Ig genes, leading the authors to conclude that the results of this case were false positive. Positive cells included cells of primary follicles, mantle zones and dendritic reticulum cells. Most cells of germinal centers appeared negative. Additionally, 198 of 297 B-cell neoplasms were shown to be light chain restricted with 127 cases expressing kappa and 71 cases expressing lambda. Of the remaining 99 cases, 74 were light chain negative and 25 were uninterpretable.[1]

Hitzman *et al.* confirmed the usefulness of immunoperoxidase staining of formalin-fixed paraffin-embedded bone marrow sections with antibodies against kappa (and lambda) light chains. Additionally, the value of utilizing these antibodies in the characterization of lymphoproliferative disorders was demonstrated. Results supported the premise that reactive plasmacytosis or lymphoid hyperplasia are generally characterized by polyclonal proliferations of cells positive for both kappa and lambda immunoglobulins and that B-cell neoplasms typically express either kappa or lambda intracellular immunoglobulins. In 10 reactive cases (5 plasmacytosis and 5 lymphocytosis cases), all were positively labeled by both kappa and lambda antibodies. In 76 bone marrow myeloma cases, 68 were monotypic (42 expressing kappa and 26 expressing lambda), one case was negative for both and 7 cases were biclonal. Of 8 lymphoma cases tested, 5 were monotypic (3 expressing kappa and 2 expressing lambda) and 3 were negative, including both of the poorly differentiated lymphocytic lymphomas. Six metastatic tumors with various origins were all negative for both kappa and lambda.[2] And, in a study involving plasmacytomas, Petruch, et al. reported that of the 46 plasmacytomas containing neoplastic plasma cells, 24 expressed kappa light chains and the other 22 expressed lambda light chains.[3]

Harris et al.[4] further substantiated the immunoreactivity of kappa and lambda in a study involving frozen sections of malignant lymphomas. They reported

that 15 out of 15 cases of nodular lymphoma were single light chain positive for either kappa (8 cases) or lambda (7 cases). Results of reactive lymph nodes did not reveal a monotypic phenotype, but instead revealed a dual expression of kappa and lambda labeling. This difference in staining allowed the differentiation of neoplastic and reactive tissues. In 31 cases of diffuse lymphoma, 24 exhibited monotypic staining for kappa (14 cases) or lambda (10 cases), 5 cases were negative for both and 2 cases were uninterpretable. In 18 cases of diffuse large cell lymphomas, kappa or lambda labeled all 16 B-cell cases (9 expressing kappa and 7 expressing lambda). Two T-cell cases were negative for both kappa and lambda.[4]

Findings reported by Mori et al. further expanded the immunoreactivity profile thus far presented for kappa (and lambda). In their study involving four cases of paraffin-embedded mantle zone lymphomas, immunohistochemistry was used to substantiate immunoglobulin phenotypes. Results revealed that all cases were monoclonal, 3 expressed kappa and 1 expressed lambda. These results were identical to those obtained from clinical serum findings. The immunoglobulin phenotype of the plasma cells surrounding the neoplastic nodules of the mantle zone lymphomas were also analyzed. In 2 cases, the plasma cells surrounding the nodules possessed the same monoclonal immunoglobulins as the neoplastic cells in the nodules. In the other 2 cases, some of the plasma cells surrounding the nodules were polyclonal, but most possessed the same monoclonal immunogobulin as the cells of the nodules.[5] In a study conducted by Meis et al.[6] in which kappa was also used as part of a panel of antibodies, formalin-fixed, paraffin-embedded Hodgkin's and non-Hodgkin's lymphomas were evaluated. In 15 cases of Hodgkin's disease, the cytoplasm of Reed-Sternberg cells reacted positively in eight cases. Five of the eight cases were polyclonal, expressing both kappa and lambda light chains. In 10 cases of T-cell lymphoma, only one case was positive, exhibiting polyclonal expression of both kappa and lambda. It was suggested that the polyclonal large lymphocytes that were positive in this case might be attributed to the presence of neoplastic transformed B-lymphocytes, as opposed to the true conserved T-cell lineage cells. Seven of 10 B-cell lymphomas reacted positively for kappa and/or lambda. Of these, 1 case was polyclonal, 4 were kappa monotypic and 2 were lambda monotypic. All six monoclonal cases were large cell B-cell lymphomas. Cytoplasmic and membranous staining of varying intensities was seen in these cases. The one polyclonal case, a B-cell immunoblastic sarcoma (large cell B-cell lymphoma), showed light cytoplasmic staining of only rare tumor cells. In two histiocytic lymphoma cases, the cytoplasm of rare tumor cells was diffusely stained for both kappa and lambda. The authors cautioned that the immunostaining of kappa (and lambda) light chains is not always specific, all of the data must be considered when developing a differential diagnosis.[6]

Hodgkin's Disease

In a study by Rabia and Kahn[7] involving immunoperoxidase labeling of kappa (and lambda) among a panel of other antibodies, 15 formalin and B-5 fixed and 5 formalin fixed cases of Hodgkin's disease were evaluated. Results with kappa and lambda revealed polytypic labeling of Reed-Sternberg cells and their monoclonal variants in 19 of the 20 cases. Such findings have lead some investigators to suggest that they are transformed lymphocytes of B-cell lineage. The remaining case demonstrated monoclonal labeling. Reactive plasma cells in all cases labeled polytypically for kappa and lambda and showed more intense cytoplasmic labeling than neoplastic cells. Most B-cell neoplasms possess monoclonal kappa or lambda light chains.

Immunoelectronmicroscopy, however, has shown the presence of kappa (and lambda), along with albumin, diffusely in the cytoplasm of Reed Sternberg cells not associated with organelles involved with protein synthesis and storage. These low molecular weight proteins may be able to cross the cell membrane whereas larger molecules may not.[8] Kadin, et al. demonstrated polyclonal Ig on the plasma membrane of Reed Sternberg cells and its internalization as well. The authors suggest this may be facilitated via Fc or complement receptors, followed by endocytosis. As a result of these observations, the B-cell origin of the Reed-Sternberg cell is not firmly established.[9]

The use of immunoperoxidase labeling for kappa (and lambda) for determining the phenotype of specific cells should be accompanied by caution and careful consideration of the entire morphological and clinical picture, particularly since the presence of kappa or lambda may be as result of passive diffusion into neoplastic cells or as result of membrane damage or active phagoctyosis.[7]

In summary, the use of immunoperoxidase labeling for kappa and lambda in a panel of antibodies is a useful tool in the differentiation and immunophenotyping of lymphomas. However, the results should be interpreted within the context of clinical data, gross and microscopic morphological criteria and multiple chemical and immunohistochemical stains. This differential approach is of particular need since it has been established that the presence of kappa (and/ or lambda) may not be solely attributable to specific staining, but may in fact be result of passive diffusion into neoplastic cells or as result of membrane damage or active phagoctyosis.[6]

Product Specific Limitations:

1. In poorly fixed tissue specimens, nonspecific staining of non-lymphoid tissues may be observed, particularly epithelium and smooth muscle.

2. Rare cases of T-cell lymphoma have been reported to stain positively for kappa and lambda light chains, polytypically. [6]

3. In Hodgkin's disease, some Reed-Sternberg cells have been reported as staining positively for kappa and/or lambda light chains.[6]

4. The use of immunoperoxidase labeling for kappa (and lambda) for determining the phenotype of specific cells should be accompanied by caution and careful consideration of the entire morphological and clinical picture, particularly since the presence of kappa or lambda may be a result of passive diffusion into neoplastic cells or as result of membrane damage or active phagoctyosis.[6]

5. Kappa and/or lambda-positive B-cells may be present in tissues other than those of lymphoid origin. Though these reactions are positive for kappa, interpretation should always be considered within the context of the predominant cell type of the tissue in question[11].

Performance Characteristics:

Reproducibility: ChemMate™ Kappa, and ChemMate™ Negative Control Reagent have been tested on serial sections of 281 tissue specimens (both normal and tumor specimens were included in the study). Runs were performed a total of three times, with each run being performed on a different day. Consistent staining results were obtained.

Immunoreactivity: Kappa and lambda polytypic expression has been reported in non-malignant lymphoid hyperplasia with positive cells including cells of primary follicles, mantle zones and dendritic reticulum cells. Additionally, kappa reactivity has been reported in B-cell lymphomas, typically as monotypic, and exceptionally as polytypic expression[10]. Some plasmacytomas have also been reported as being reactive for kappa. For a more comprehensive review of reported kappa immunoreactivity, please refer to the Summary and Explanation and Product Specific Limitations sections.

References:

1. Picker L, et al. Immunophenotypic criteria for the diagnosis of non-Hodgkin's lymphoma. Am J Path. 1987, 128:181
2. Hitzman J, et al. Immunoperoxidase staining of bone marrow sections. Cancer. 1981, 48:2438
3. Pertruch U, et al. Frequent expression of haemopoietic and non-haemopoietic antigens by neoplastic plasma cells. An immunohistochemical study using formalin-fixed, paraffin-embedded tissue. Histopath. 1992, 20:35

4. Harris N, et al. Demonstration of immunoglobulin in malignant lymphomas. Am J Clin Path. 1982, 78:14
5. Mori N, et al. Immunohistochemical study of mantle zone lymphoma. Am J Clin Path. 1988, 89:143
6. Meis J, et al. A comprehensive marker study of large cell lymphoma, Hodgkin's disease and true histiocytic lymphoma in paraffin-embedded tissue. Am J Clin Path. 1986, 86:591
7. Rabia M and Kahn L. Immunohistochemistry of Hodgkin's disease. Cancer. 1983, 52:2064
8. Poppema S, et al. The significance of intracytoplasmic proteins in Reed-Sternberg cells. Cancer. 1978, 42:1793
9. Kadin ME, et al. Exogenous immunoglobulin and the macrophage origin of Reed-Sternberg cells in Hodgkin's disease. N Engl J Med. 1978, 299:1208
10. Cleary ML, et al. Monoclonality of lymphoproliferative lesions in cardiac-transplant recipients. NEJM 1984; 310:477
11. Ernst PB, et al. Immunity in mucosal tissues. Basic and Clinical Immunology, 6th edition, chapter 12. Stites, DP, et al. Editors. Norwalk, CT, Appleton & Lang Press, 1987:159

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

OCT - 3 1997

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Re: K973391
Trade Name: ChemMate™ Kappa
Regulatory Class: II
Product Code: DEM
Dated: July 7, 1997
Received: July 10, 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 (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): K973391

Device Name: ChemMate Kappa
Antibody Reagent

Indications For Use:

To qualitatively aid in the identification by light microscopy of human cells of lymphoid origin, by recognizing kappa light chains in immunoglobulin secreting plasma cells and plasmacytoid B lymphocytes, in normal and pathologic paraffin embedded tissues precessed in neutral buffered formalin, B5, or Bouin's fixative. Positive results aid in the differential diagnosis, classification and immunophenotyping of lymphomas and must be interpreted by a pathologist within the context of clinical data, gross and microscopic morphological criteria and multiple chemical and immunohistochemical stains.

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

...ion Sign-Off)
...n of Clinical Laboratory Devices
...) Number

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

(Optional Format 1-2-96)