

K413584

510(k) Summary

OCT - 3 1997

Date: September 29, 1997

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Registration #: 2028492

Trade Name: ChemMate™ UCHL1

Class II

Intended Use: FOR IN VITRO DIAGNOSTIC USE.

ChemMate™ UCHL1 (CD45RO) is intended for laboratory use to qualitatively identify by light microscopy human lymphocytes of T-cell lineage in normal and pathological paraffin embedded tissues processed in zinc formalin, neutral buffered formalin, Bouin's or B5 fixative. Positive results aid in the classification of lymphomas as T-cell in origin 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 mouse monoclonal antibody has been optimally prediluted for use with the ChemMate™ SDK605 Secondary Detection - Peroxidase/DAB kit. Additionally, the prediluted ChemMate™ UCHL1 (CD45RO) 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™ UCHL1 (CD45RO) is comprised of a mouse monoclonal antibody, clone UCHL1, and is of the IgG2a, Kappa light chain class of immunoglobulins<sup>1</sup>. The antibody reacts with the 180kD low molecular weight isoform of CD45 or leukocyte common antigen (LCA/CD45) family.<sup>2,3</sup> The 180kD glycoprotein occurs on most thymocytes and activated T cells, and on a proportion of resting T cells. Additionally the antibody is reactive with a subpopulation of resting T cells within both the CD4 and CD8 subsets.<sup>4</sup> Granulocytes and monocytes are also reactive with UCHL1 while most normal B cells and NK cells are unreactive.<sup>1,5</sup> UCHL1 has been classified as a CD45RO antibody by the Fourth International Workshop on Human Leukocyte Differentiation Antigens.<sup>5</sup>

In a broad study, Smith et al. utilized fluorescent activated cell sorting techniques with UCHL1 to outline the reactivity of this antibody. UCHL1 was shown to stain granulocytes, monocytes, most thymocytes, 72% of CD4+ cells 36% of CD8+ cells, a number of T-cell lines and some neoplastic B-cell lines. Normal B-cell and NK cells were unreactive. On frozen sections of tonsil and spleen, UCHL1 labeled cells in known T-cell areas. The authors concluded that UCHL1 detects a subset of T-cells and may be useful in studying immune disorders by detecting changes in T-cell subsets.<sup>1</sup> Poppema et al. also reviewed the immunoreactivity of UCHL1 on normal lymphoid tissues and lymphomas as well as lymphocyte cytopsin preps and LCA transfected cell lines. Their results with UCHL1 demonstrated reactivity with 60% of cells in T-cell areas of spleen, tonsil and lymph nodes and primarily with cortical thymocytes of the thymus. Additionally UCHL1 strongly stained peripheral blood monocytes and granulocytes. It was further noted that UCHL1 recognized a 180 kD band on a Western blot and was positive in 10 of the 12 T-cell lymphomas.<sup>7</sup> In a study involving a panel of antibodies on paraffin-embedded fixed tissue, UCHL1 was employed by Linder et al. They also reported that UCHL1 positively labeled T-lymphocytes in human tonsil and specifically, greatly labeled greater than 75% of interfollicular cells, less than 10% of the follicular mantle cells, and weakly labeled less than 10% of the cells in the germinal centers.<sup>8</sup>

Wieczorek, et al. employed UCHL1 in an immunohistochemical study on routinely fixed paraffin-embedded tissues known to contain neoplastic T cells. UCHL1 was reactive in both formalin and Bouin's fixed paraffin-embedded tissues. Further, the antibody was positive in 17 out of 28 T-cell non Hodgkin's lymphomas tested, only 1 of 17 Hodgkin's disease cases and only 2 of the 35 B-cell non-Hodgkin's lymphoma cases examined.<sup>9</sup>

Using 50 formalin-fixed paraffin-embedded archival cases of T-cell lymphomas, previously diagnosed by immunochemistry and/or gene rearrangement, Cabecadas and Isaacson further characterized those T-cell lymphomas by low or high grade and histological type. While the lymphomas were heterogenous for a number of antibodies used in the panel, results with UCHL1 revealed positive membrane staining in 47 out of 50 cases.<sup>10</sup> Further, Shin et al. were able to determine the immunophenotypes of Reed-Sternberg (RS)-like cells upon re-analysis of 19 low-grade lymphomas using immunohistochemistry. Previously linked to high-grade lymphoma and resembling true Reed-Sternberg cells of Hodgkin's disease, the Reed-Sternberg-like cells were successfully identified with immunohistochemical results as re-transformed neoplastic cells of B-cell lineage. Accordingly, UCHL1 was unreactive in all of these low grade lymphomas.<sup>11</sup> And in a study involving 49 formalin-fixed and paraffin-embedded cutaneous malignant lymphomas and disorders, diagnosed by histologic criteria, Hauschild and Sterry determined 29 of these cases to be T-cell lymphomas. UCHL-1 was reactive with 27 of the 29 T-cell lymphomas as follows: 12 of 12 mycosis fungoides lymphomas, 12 of 12 pleomorphic T-cell lymphomas, 2 of 2 Sezary's Syndrome and with 1 of 3 large anaplastic T-cell lymphomas.<sup>12</sup> Clark et al. employed UCHL1 on B-5 fixed paraffin-embedded reactive or neoplastic lymphoid and hematopoietic proliferative disorders, diagnosed by histologic criteria. They reported that UCHL1 labeled 29 of 37 T-cell lymphomas and only 1 of 54 B-cell neoplasms. Additionally, UCHL1 was negative in all Hodgkin's disease with 24 of 32 cases exhibiting Reed-Sternberg cell-nonreactivity and 8 of 32 cases exhibiting variable Reed-Sternberg-cell positivity. Only 1 of 15 leukemias stained positively with UCHL1. In the reactive lymph nodes, UCHL1 labeled cells in the interfollicular areas and sparsely labeled cells in follicular centers and the mantle zone. Dermatopathic T-zone nodules showed less than 25% of cells as UCHL1 positive.<sup>13</sup>

Using a small panel of antibodies, including UCHL1, Segal et al. also conducted a study encompassing B-5 fixed, paraffin-embedded neoplastic and lymphoid proliferative diseases. All cases had been previously immunotyped through immunohistochemistry and genotypic analyses. UCHL1 was reactive in 0 of the 74 B-cell malignant lymphomas and was reactive in 3 of the 5 malignant T-cell lymphomas.<sup>14</sup> Additionally, Andrade et al. used a panel of antibodies, including UCHL1 to immunophenotype hematopoietic malignancies. These cases had been originally phenotyped in cell suspensions or frozen sections by direct and indirect immunofluorescence. UCHL1 was unreactive in 27 neoplasms of B-cell origin, 4 cases of extramedullary leukemia, 5 cases of Hodgkin's disease and 5 cases of histiocytic neoplasms and reactive in 9 of 11 T-cell lymphomas.<sup>15</sup> Macon et al. reported that UCHL1 was reactive in 53 of 77 peripheral T-cell

lymphomas and reactive in only 3 of 39 B-cell lymphomas and 3 of 11 Hodgkin's lymphomas.<sup>16</sup> Further, in a study which encompassed 28 cases of Hodgkin's disease and anaplastic large cell lymphomas (ALCL), Leoncini et al. employed histologic diagnosis to demonstrate that UCHL1 was positive in 1 of 13 Hodgkin's disease whereas it positively labeled 5 of 11 cases of ALCL. UCHL1 was positive in 1 of the remaining 4 cases of undetermined status.<sup>17</sup> Myskow et al. applied a panel of monoclonal antibodies, including UCHL1 to a series of formalin-fixed paraffin-embedded B and T cell non-Hodgkin's lymphomas of various subtypes that had been characterized previously by frozen-section immunophenotyping. UCHL1 was reactive in 2 of 14 low grade B-cell lymphomas and 8 of 30 high-grade B-cell lymphomas, including 7 of 14 centroblastic (large non-cleaved cell) lymphomas. Additionally, UCHL1 positively labeled 23 of 32 T-cell lymphomas.<sup>18</sup> And, Ngan et al. used a panel of antibodies, including UCHL1, on paraffin sections of non-Hodgkin's lymphoma that had been previously diagnosed based on immunohistochemical staining of cryostat sections. Results revealed that UCHL1 was unreactive in all 77 of the B-cell lineage lymphomas.<sup>19</sup>

Consistent with its cross-reactivity with myeloid lineage cells, UCHL-1 positive membrane staining has been noted with mature myeloid cells in granulocytic sarcomas, and macrophages in histiocytic lymphomas, malignant histiocytosis of the intestine and Langerhans Cell histiocytosis<sup>20, 24</sup>. Morphological studies and the use of UCHL-1 in a panel of antibodies are recommended for use in the differential diagnosis of granulocytic sarcoma, plasmacytoma, and histiocytic neoplasia from T-cell lymphomas.

In summary, UCHL1, is a useful aid in the diagnosis of neoplasms of T cell lineage. However, it does not stain all T cell lymphomas and does stain some lymphomas of B cell origin. This antibody is a useful tool in the differential diagnosis of lymphomas when used as a part of a panel of appropriate antibodies.

#### **Product Specific Limitations:**

1. In poorly fixed tissue specimens, nonspecific staining of non-lymphoid tissues may be observed, particularly epithelium and smooth muscle.
2. Occasional cases of T-cell lymphoma have been reported to co-express the CD45RO antigen.
3. It is important to differentiate between the ring-like membrane staining pattern associated with a T-cell lineage and the nonspecific cytoplasmic and nuclear staining. Nuclear staining may represent cross-reactivity with an unknown nuclear antigen.<sup>26</sup> Nonspecific cytoplasmic staining has been reported in smooth muscle, hepatocytes, squamous and transitional

epithelium, gall bladder and breast tissue.<sup>20</sup> No other UCHL1 reactivity has been noted with normal or malignant non-lymphoid cells.<sup>8</sup>

4. Staining has been detected in select groups of B-cell pathological tissues. A few cases of diffuse large cell (9/50, 18%) non-Hodgkin's B-Cell lymphomas coexpress the CD45RO antigen<sup>6, 8, 13</sup>. One group<sup>8</sup> has reported weak membrane staining in scattered Reed-Sternberg cells in some cases of Hodgkin's Disease (8/32, 25%), while other groups report no staining of Reed-Sternberg cells.<sup>8, 20</sup> Petruch et al.,<sup>21</sup> reported UCHL1 positive neoplastic plasma cells in 24/51 (47%) of plasmacytomas/multiple myelomas tested. Weak, nonspecific cytoplasmic staining may also be seen in some large cell lymphomas of B-cell origin and myelomas.<sup>6, 20</sup>
5. In Hodgkin's disease, Reed-Sternberg cells are predominantly negative for UCHL1. However, there have been some reports of variable positive staining with UCHL1 in Reed-Sternberg cells.<sup>8, 9, 13, 14</sup>
6. UCHL1-positive B-cells may be present in tissues other than those of lymphoid origin. Though these reactions are positive for UCHL1, interpretation should always be considered within the context of the predominant cell type of the tissue in question.
7. Occasional staining of intraluminal secretions, surface epithelium and cytoplasm has been reported in breast fibroadenoma and fibrocystic disease with DAKO<sup>®</sup> CD45<sup>25</sup> and DAKO<sup>®</sup> CD45RO, UCHL-1 antibodies.
8. Because UCHL1 does not stain all T-cells, the absence of staining does not exclude the absence of T-cell lineage. This antibody is a useful tool as long as it is used as a part of a panel of antibodies.

#### **Performance Characteristics:**

**Reproducibility:** ChemMate™ UCHL1 (CD45RO) has been tested on serial sections of tissue specimens. Consistent staining results have been obtained with run to run and within run antibody testing.

**Immunoreactivity:** The following immunoreactivities have been demonstrated in paraffin-embedded tissues.. The list provided below is not exhaustive but characterizes the types of immunoreactivity reported in the literature for the UCHL1 clone contained in the monoclonal antibody cocktail of the ChemMate™ UCHL1 (CD45RO).

**TABLE I REACTIVE NORMAL TISSUES/CELLS**<sup>1,4,5,7,8,10</sup>

<b>Tissues</b>	<b>Cells</b>
<p>*Lymph Node:  germinal center T-cells  mantle zone lymphocytes (most cells)</p>	<p>Thymocytes:  activated T cells  resting T cells</p>
<p>*Spleen:  white pulp areas    periarteriolar lymphatic sheath  red pulp areas    granulocytes    monocytes</p>	<p>Granulocytes   Monocytes</p>
<p>*Tonsil:  germinal center T-cells    (scattered positive)  interfollicular T-cells  follicular mantle T lymphocytes    (scattered positive)</p>	
<p>*Thymus:  cortical thymocytes  medullary thymocytes (scattered)</p>	
<p>Whole Blood (Peripheral):  circulating T lymphocytes  monocytes</p>	
<p>Cytospins of peripheral blood:  monocytes  granulocytes  macrophages</p>	

\* In paraffin embedded tissue<sup>7, 8, 10</sup>

**TABLE II NONREACTIVE NORMAL TISSUES/CELLS<sup>1,7,8,12</sup>**

<b>Non-Lymphoid Tissues</b>
Thyroid
Lung
Breast
Pancreas
Liver
Prostate
Kidney
Uterus
Muscle

**TABLE III NEGATIVE NON-LYMPHOID PATHOLOGICAL  
TISSUES/CELLS<sup>8, 22, 23</sup>**

<p><b>Epithelial</b></p> <p>Adenocarcinoma: Breast Colon Lung Ovary Prostate Thyroid</p> <p>Ameloblastoma</p> <p>Carcinoma: Squamous cell Uterine Cervix Lung Skin Small cell Non-keratinizing Undifferentiated</p> <p>Mesothelioma</p> <p>Melanoma</p> <p><b>Mesenchymal</b></p> <p>Chondrosarcoma, extraskeletal myxoid</p> <p>Malignant Fibrous Histiocytoma</p> <p>Rhabdomyosarcoma Alveolar</p>	<p><b>Endocrine</b></p> <p>Neuroendocrine: Thyroid, medullary carcinoma</p> <p>Mixed</p> <p>Neuro: Anaplastic astrocytoma Neurofibroma Neuroblastoma</p> <p>Small Cell Tumors: Ewings Sarcoma</p>
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Case numbers not reported for the majority of the cases listed above.

**TABLE IV: NON-HODGKIN'S LYMPHOMAS and OTHER LYMPHOPROLIFERATIVE DISORDERS**

TISSUE	T-CELL	%	95% CI	B-CELL	%	95% CI
Non-Hodgkin's Lymphomas:	266/394	68%	63-72.5%	42/461	9%	7.0-12.5%
T-Cell Lymphoma: <sup>7,8,12,13,15,16,18,19</sup>	73/92	79%	68.5-87%	0/4	--	0-60.2%
-Unspecified	40/51	78%	64-88.5%	0/4	--	0-60.2%
-Cutaneous	19/24	79%	57.5-92.5%			
-Mycosis Fungoides	14/17	82%	56-96%			
Low Grade: <sup>8,9,10,11,12,13,15,16,18,19,22</sup>	87/117	74%	65-82%	7/256	3%	2.0-6.5%
-Small Lymphocytic	19/23	83%	62-95%	1/40	3%	0.1-14%
-Follicular center cell				3/77	4%	1.0-12%
-Small cleaved, follicular & diffuse	8/9	89%	50-99.5%	0/60	--	0-6.5%
-Mixed, diffuse	48/61	79%	67-88%	1/12	8%	0.8-38%
-Large cleaved				0/3	--	0-70.8%
-Large diffuse	12/24	50%	22-78%	2/55	4%	0.9-13.5%
-Large follicular				0/9	--	0-34%
Intermediate:	11/13	85%	57-97%	2/64	3%	0.5-10.5%
-Large cell	3/5	60%	19-92%	1/38	3%	0.2-18%
-Cleaved, diffuse	4/4	100%	39.8-100%	0/6	--	0-45.9%
-Mixed, diffuse	3/3	100%	29.2-100%	0/2	--	0-84.7%
-Large, diffuse	1/1	100%	--	1/18	6%	0.1-28%
High Grade: <sup>8,9,10,12,14,15,16,17,18</sup>	56/102	55%	48-64%	8/122	7%	3.5-13%
-Small non-cleaved				1/8	12.5%	0.5-53%
-Large immunoblastic	25/40	63%	47-78%	0/23	--	0-14%
-Immunoblastic clear cell	6/17	35%	13.5-62%			
-Large lymphoblastic	10/19	53%	29.5-75.5%	0/3	--	0-70.8%
-Malignant	6/8	75%	33.5-96.5%	7/88	8%	4-16.5%
-Anaplastic, large	9/18	50%	27-74%			
Miscellaneous: <sup>12,13,14,15,16,18,21</sup>	35/49	71%	53-82.5%	1/10	10%	0.5-54%
-Sezary's Syndrome	2/2	100%	15.8-100%			
-Immunoblastic Sarcoma	20/25	80%	56-94%	0/5	--	0-52%
-Marginal Zone Lymphoma				0/1	--	--
-Sinonasal Large-Cell Lymphoma	7/16	44%	20-70.5%	1/1	--	--
-Monocytoid Lymphoma				0/3	--	0-70.8%
-Lennert's Syndrome	6/6	100%	54.1-100%			
Other Lymphoproliferative Disorders:	4/21	19%	5.5-42%	24/59	41%	28-54%
-Acute Myelogenous Leukemia	0/1	--	--	0/1	--	--
-Chronic Myelogenous Leukemia	0/3	--	0-70.8%	0/1	--	--
-Hairy Cell Leukemia	0/2	--	0-84.7%			
-Plasmacytoma/Plasma Cell Myeloma				24/57	42%	29-56%
-Malignant Histiocytes of Intestine	4/15	27%	13-55%			

Note: The number of reactive tissues over the total number of tissues is recorded by the specimen type. Confidence Intervals have been assigned for sample values greater than 1.

**TABLE V HODGKIN'S LYMPHOMA** <sup>9,12,13,14,15,16,17</sup>

TISSUE	NO. REACTIVE / NO. TESTED	%	95% CONFIDENCE INTERVAL
Lymphocyte Depleted	0/4	----	0-60.2%
Lymphocyte Predominant	2/6	33%	1.7-98%
Mixed Cellularity	4/19	21%	7-45.4%
Nodular Sclerosing	4/54	7.4%	2.5-18%
Unclassified	2/6	33%	1.7-98%
<b>Total:</b>	12/89	13%	7.5-22.5%

The majority of cases presented with UCHL1-negative Reed-Sternberg cells. Although Reed-Sternberg cells predominantly are unreactive for UCHL1, occasional, scattered positive reactions were mentioned.

Note: The number of reactive tissues over the total number of tissues is recorded by the specimen type. Confidence Intervals have been assigned for sample values greater than 1.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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OCT - 3 1997

Re: K973389  
Trade Name: ChemMate™ UCHL1  
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 (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 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 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.

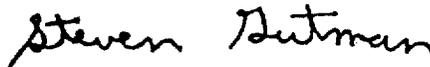
Page 2

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 I. Gutman, M.D., M.B.A.  
Director  
Division of Clinical  
Laboratory Devices  
Office of Device Evaluation  
Center for Devices and Radiological Health

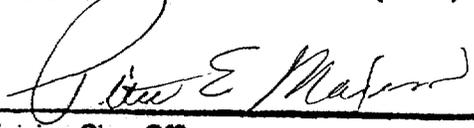
Enclosure

Page 1 of 1510(k) Number (if known): K973389Device Name: ChemMate UCHL1 (CD45RO)Antibody Reagent**Indications For Use:**

To qualitatively aid in the identification by light microscopy of human cells of T-cell lineage, by recognizing CD45RO antigen in normal and pathologic paraffin embedded tissues processed in neutral buffered formalin, B5, or Bouin's fixative. Positive results aid in the classification of lymphomas as T-cell in origin and must be interpreted by a pathologist within the context of clinical data, gross and microscopic morphological criteria and multiple chemical and immunochemical stains.

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

  
 (Division Sign-Off)  
 Division of Clinical Laboratory Devices  
 510(k) Number K973389

Prescription Use   
 (Per 21 CFR 801.109)

OR

Over-The-Counter Use 

(Optional Format 1-2-96)