

K4 13340

510(k) Summary

OCT - 3 1997

Date: September 29, 1997

VENTANA MEDICAL SYSTEMS, INC.  
3865 North Business Center Drive  
Tucson, Arizona 85705

Telephone: (520) 887-2155  
Facsimile: (520) 887-2558

Contact: Stephen A. Tillson, Ph.D.  
Vice President Scientific Affairs/ Quality Assurance

Registration #: 2028492

Trade Name: ChemMate™ L26 (CD20)

Class II

Intended Use: FOR IN VITRO DIAGNOSTIC USE.

The ChemMate™ L26 (CD20) is intended for laboratory use to qualitatively identify by light microscopy human lymphocytes of B-cell lineage in normal and pathological paraffin embedded tissues processed in zinc formalin, neutral buffered formalin, Bouin's or B5 fixative.<sup>9, 12, 16, 19</sup> Positive results aid in the classification of lymphomas as B-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 or SDK305 Secondary Detection - Peroxidase/DAB kit. Additionally, the prediluted ChemMate™ L26 (CD20) antibody as well as the ChemMate™ SDK605 or SDK305 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

The ChemMate™ L26 (CD20) is comprised of a mouse monoclonal antibody, clone L26, and is of the IgG2a / Kappa light chain class of immunoglobulins.<sup>1,2,3</sup> The antibody reacts with two non-covalently associated components (33kD and 30kD) present in the majority of B-cells.<sup>1,2</sup> Positive staining occurs on the cells' plasma membrane. Recent studies demonstrated that the L26 antibody positively stained COS-1 cells transfected with cDNA encoding for the CD20 antigen (a pan B-cell marker).<sup>4</sup> L26 has been classified as a CD20 antibody by the Fifth International Workshop on Human Leukocyte Differentiation Antigens.<sup>5</sup>

A unique feature of the ChemMate™ L26 (CD20) is the antibody's ability to recognize epitopes on lymphocytes that survive the rigors of processing and fixation.<sup>2,3,6</sup> The resultant advantage in the use of this antibody is its applicability with formalin-fixed specimens.

The CD20 antigen is expressed in most B-cells present in peripheral blood and lymphoid tissue including germinal center blasts, mantle zone lymphocytes and scattered interfollicular lymphocytes.<sup>7-9</sup> Staining also occurs in most non-Hodgkin's lymphomas of B-cell lineage.<sup>3,10</sup>

In a study encompassing benign lymphoid tissues, Cartun et. al. demonstrated that L26 was reactive in known B-cell rich regions; i.e. germinal centers, mantle zone lymphocytes of lymph node and tonsil and white pulp of spleen. Thymus and bone marrow were unreactive for L26 with only scattered positive cells in the medulla regions of thymus. L26 was unreactive in all normal non-lymphoid tissues tested and negative in 124 non-lymphoid tumors with L26 reactivity confined to immunoreactive lymphocytes infiltrated within the tumors. Among non-Hodgkin's lymphoma cases, L26 was shown to be reactive in 73 out of 74 B-cell lymphomas, including 44 out of 44 cases of diffuse large cell and immunoblastic B-cell lymphoma. Only 37 of 44 of these B cell Lymphomas were positive with leukocyte Common Antigen (LCA). This finding suggests that a panel of antibodies including L26 should be used to exclude B-cell pathogenesis. No T-cell tumors (0/8) were reactive. Four of four hairy cell leukemias were positive for L26.<sup>7</sup>

The majority of non-Hodgkin's lymphomas will stain positively for L26. Elghetany, et al. reported on 44 cases of paraffin-embedded non-Hodgkin's lymphomas stained with a panel of monoclonal antibodies to T and B cells. Results revealed that immunophenotyping was the same as genotypic analysis in 37 of the 39 cases. Five could not be assigned a specific B or T-

cell lineage. L26 labeled 32 out of 33 B-cell lymphomas and one of the six T-cell lymphomas.<sup>8</sup> In a study on 13 diffuse mixed cell non-Hodgkin's lymphomas, Katzin et al. employed immunohistochemical and gene rearrangement analyses to determine whether these mixed cell lymphomas were of monoclonal, oligoclonal or dual lineage. Large lymphoid cells were L26 positive in 12 of 13 cases and in no cases were the small lymphoid cells positive for L26.<sup>11</sup>

And in studies conducted by Wolf et al. in which thyroid neoplasms were re-evaluated, immunophenotyping results showed that 65 of the 68 neoplasms assessed were non-Hodgkin's lymphomas (60 out of 65 were immunoreactive with L26). Of these lymphomas, 63 out of 65 were determined to be of B-cell origin and two were not able to be determined. The remaining three cases were characterized as epithelial in origin (carcinomas) and negative for L26. Immunohistochemical results converted a preliminary diagnosis of small cell carcinoma to a non-Hodgkin's lymphoma in many cases. Small cell carcinomas are rare in the thyroid with most thyroid neoplasms being lymphomas of B-cell origin.<sup>12</sup>

Additionally, Hodgkin's disease that has been classified as lymphocyte predominance stained positively for L26. Nicholas, et al re-evaluated archival cases previously diagnosed as lymphocyte predominance Hodgkin's disease (LPHD) using a panel of antibodies, including L26. Immunostaining revealed that of the 30 cases all were positive for L26. These cases were further subdivided as LPHD with nodular architecture (21 cases), diffuse LPHD (four cases) and LPHD with inconspicuous nodularity. Mixed cellularity Hodgkin's (13 cases), nodular sclerosing Hodgkin's (two cases), and interfollicular Hodgkin's (one case) were all negative for L26. Additionally, the LPHD biopsies all contained polylobated Reed-Sternberg cell variants that were positive for L26.<sup>13</sup>

L26 reactivity has been reported in several neoplastic and lymphoproliferative disorders. In a study encompassing 110 B-5 fixed, paraffin-embedded neoplastic and lymphoid proliferative disorders, Segal et. al. confirmed L26 reactivity in 73 of the 76 B-cell lymphomas and found L26 was unreactive in 5/5 T-cell lymphomas. Additionally, 11 of 12 cases positive for the T-cell marker CD43 were also positive for L26, indicating a differentiation of malignant B-cell lymphoma.<sup>14</sup>

Reactivity of L26 with hairy cell leukemias and monocytoid B-cell lymphomas was further assessed by Stroup, et al. by using a large panel of antibodies in 42 cases of hairy cell leukemia (HCL) and 24 cases of monocytoid B-cell lymphoma (MBCL). L26 was immunoreactive in 85% of the hairy cell leukemias tested. Similarly, L26 was positive in 84% of the monocytoid B-cell lymphomas tested.<sup>15</sup>

A panel of antibodies, including L26, were used by Wolf et al. to stain 34 paraffin-embedded cases of gastrointestinal tract lymphoma. Previous phenotyping studies through extensive frozen section immunohistochemistry revealed that 31 of the 34 cases were B-cell in origin and the remaining three T-cell in origin. 24 of the 31 paraffin sections were immunoreactive with L26 and L26 was negative in all three of the T-cell lymphomas.<sup>16</sup>

Further, in studies conducted by Macon, et al. L26 labeled 33 out of 38 B-cell lymphomas tested and 0 out of 76 peripheral T-cell lymphomas.<sup>17</sup>

No L26 cross reactivity has been observed with normal or malignant non-lymphoid cells with the following exception<sup>7, 20</sup>. L26 positive dendritic cells have been noted in the medulla of normal thymi and thymomas along with scattered B-Cells<sup>19, 23, 24</sup>. The L26 positive dendritic cells coexpress keratin and are frequently associated with Hassall's corpuscles. It is recommended that an epithelial marker, such as keratin, be used in conjunction with the L26 antibody to aid in the differential diagnosis of mediastinal non-Hodgkin's lymphomas.

A summary of immunoreactivity in lymphoid and hematopoietic cells/tissues and neoplasms may be found in tables I-V of Performance Characteristics in this insert.

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

1. A few cases of diffuse large (2/26, 7.7%) and diffuse mixed (1/12, 8.3%) non-Hodgkin's T-Cell lymphomas coexpress the CD20 antigen<sup>10, 20</sup>.
2. In poorly fixed tissue specimens, nonspecific staining of non-lymphoid tissues may be observed, particularly epithelium and smooth muscle.
3. In some cases of Hodgkin's disease, particularly the lymphocyte predominant type, membrane, cytoplasmic, or paranuclear staining of some Reed-Sternberg cells has been observed<sup>5, 7</sup>.
4. The differential diagnosis of mediastinal tumors with the L26 antibody may be compromised by the presence of L26 and keratin positive dendritic cells found in the medulla of normal thymi and some thymomas<sup>19, 23, 24</sup>. Use a panel of antibodies to distinguish mediastinal tumors.
5. No L26 cross-reactivity has been observed with normal or malignant non-lymphoid cells with the following exception<sup>7, 20</sup>. L26 positive dendritic cells have been noted in the medulla of normal thymi and thymomas along with

scattered B-Cells<sup>19, 23, 24</sup>. The L26 positive dendritic cells coexpress keratin and are frequently associated with Hassall's corpuscles. It is recommended that an epithelial marker, such as keratin, be used in conjunction with L26 antibody to aid in the differential diagnosis of mediastinal non-Hodgkin's lymphomas.

6. Dako® CD20, L26 positive B-Cells have been observed in granulomatous lesions of unknown significance, granulomas associated with toxoplasmosis; and sarcoid reaction affiliated with seminoma, Hodgkin's Disease, non-Hodgkin's lymphoma, and cancer of the breast, colon, and lung<sup>25</sup>.
7. Occasional cases of T-cell lymphoma have been reported to co-express the CD20 antigen.
8. In Hodgkin's disease, Reed-Sternberg cells have been reported as staining positively for L26.<sup>13,14</sup>
9. L26-positive B-cells may be present in tissues other than those of lymphoid origin. Though these reactions are positive for L26, interpretation should always be considered within the context of the predominant cell type of the tissue in question<sup>26</sup>.

#### **Performance Characteristics:**

Reproducibility: ChemMate™ L26 (CD20), and 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 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 L26 clone contained in ChemMate™ L26 (CD20).

**TABLE I REACTIVE NORMAL TISSUES/CELLS** <sup>7,8,9</sup>

<b>Tissues</b>
Lymph Node: germinal center cells mantle zone lymphocytes (most cells)
Spleen: white pulp (B-cell) areas
Tonsil: germinal center cells mantle zone lymphocytes (most cells)
Thymus: medulla (some scattered areas)*
Whole Blood (Peripheral): circulating B lymphocytes

\* L26 positive dendritic cells have also been identified<sup>19, 23, 24</sup>

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

<b>Lymphoid Tissues</b>	<b>Non-Lymphoid Tissues</b>
<p><b>Lymph Node:</b> Interfollicular &amp; Medullary Areas* Histiocytes (Interdigitating Reticulum Cells) Dendritic Reticulum Cells, Sinus Histiocytes</p> <p><b>Spleen:</b> Red pulp areas*</p> <p><b>Tonsil:</b> Interfollicular &amp; Medullary Areas* Histiocytes (Interdigitating Reticulum Cells) Dendritic Reticulum Cells, Sinus Histiocytes</p> <p><b>Thymus:</b> Cortex*</p> <p><b>Bone Marrow:</b> Erythroid Cells Myeloid Cells Megakaryocytes</p>	<p><b>Skin:</b> Epidermis Sebaceous Glands Eccrine Glands Hair Follicles</p> <p><b>Thyroid:</b> Follicular Epithelium</p> <p><b>Lung:</b> Pneumocytes Bronchial Epithelium</p> <p><b>Brain:</b> Neurons Glial Cells</p> <p><b>Pancreas:</b> Acini Intercalated &amp; Interlobular Ducts Islets</p> <p><b>Liver:</b> Hepatocytes Bile Duct Epithelium</p> <p><b>Prostate:</b> Epithelial Glands Stroma</p> <p><b>Kidney:</b> Proximal Convoluted Tubules Distal Convoluted Tubules Glomeruli Collecting Ducts</p> <p><b>Uterus:</b> Endometrium Myometrium Ectocervix Endocervix</p> <p><b>Muscle:</b> Cardiac Smooth Skeletal</p> <p><b>Placenta</b></p> <p><b>Other:</b> Fibroblasts Mesothelium</p> <p><b>Peripheral Blood:</b> Erythrocytes Granulocytes Monocytes Platelets Most T-cells</p>

\*Scatted positive B-cells identified

**TABLE II NON-LYMPHOID PATHOLOGICAL NEGATIVE  
TISSUES/CELLS<sup>7,9,12,20</sup>**

<b>Epithelial (0/90):</b>	<b>Endocrine (0/24):</b>
Adenoma, Parathyroid (0/1)	Neuroendocrine (0/21)
Adenocarcinoma (0/49):	Carcinoid (0/5)
Breast (0/11)	Lung, small cell undifferentiated (0/5)
Colon(0/7)	Merkel cell tumor (0/4)
Liver, hepatocellular (0/5)	Pancreas (0/3)
Lung (0/10)	Thyroid, medullary carcinoma (0/4)
Metastatic (0/4)	Other (0/3)
Ovary (0/1)	Pituitary adenoma (0/1)
Ovary, cystadenocarcinoma (0/2)	Prolactinoma (0/2)
Pancreas (0/1)	Mixed (0/5):
Stomach (0/3)	Carcinoma, Salivary Gland (0/1)
Thyroid (0/3)	Fibroadenoma, breast (0/3)
Thyroid, papillary (0/2)	Uterus (0/1)
Ameloblastoma (0/1)	Neuro/Glial (0/9):
Carcinoma (0/20):	Astrocytoma (0/5)
Bladder, transitional cell (0/5)	Glioma, malignant (0/2)
Nasopharyngeal (0/1)	Ganglioneuroma (0/1)
Squamous cell (0/10)	Neurofibroma (0/1)
Small cell (0/3)	Small Cell Tumors (0/9):
Thyroid, anaplastic (0/1)	Ewing's Sarcoma (0/4)
Mesothelioma (0/5)	Neuroblastoma (0/4)
Melanoma (0/14):	Wilm's (0/1)
Amelanotic (0/10)	
Unspecified (0/4)	
<b>Mesenchymal (0/25):</b>	
Angiosarcoma (0/3)	
Chordoma (0/1)	
Chondrosarcoma, extraskeletal myxoid (0/1)	
Endometrial Stromal Sarcoma (0/3)	
Fibrosarcoma (0/1)	
Leiomyosarcoma (0/3)	
Malignant Fibrous Histiocytoma (0/6)	
Rhabdomyosarcoma (0/7)	
Embryonal (0/2)	
Unspecified (0/5)	

Note: None of the 139 non-lymphoid pathological tissues listed above were reactive for L26. 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: 0/2 = 0-84.2%, 0/3 = 0-70.8%, 0/5 = 0-52.2%, 0/7 = 0-41.0%, 0/9 = 0-33.6%, 0/10 = 0-30.8%, 0/14 = 0-23.2%, 0/17 = 0-19.5%, 0/21 = 0-16.1%, 0/24 = 0-14.2% 0/25 = 0-13.7%, 0/61 = 0-6 %, 0/99 = 0-3.5%

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

<b>Tissue</b>	<b>B-Cell</b>	<b>%</b>	<b>95% CI</b>	<b>T-Cell</b>	<b>%</b>	<b>95% CI</b>
<b>Non-Hodgkin's Lymphoma</b>	<b>397/430</b>	<b>92%</b>		<b>1/89</b>	<b>1.1%</b>	<b>0.2-4.5%</b>
<b>Low Grade:</b> <sup>7,10,11,17,21</sup>	<b>176/184</b>	<b>96%</b>	<b>93.5 98.5%</b>	--	--	
-Small Lymphocytic	26/32	81%	63-93%	--	--	
-Small cleaved, follicular & diffuse	47/47	100%	92-100%	0/5	--	0-52%
-Mixed small and large	7/7	100%	59-100%	1/22	4.5%	0.7-27%
-Large cleaved	2/2	100%	15.8-100%	--	--	
-Large diffuse	94/96	98%	93-99.8%	0/13	--	0-24.7%
<b>Intermediate:</b> <sup>7,21</sup>	<b>25/25</b>	<b>100%</b>	<b>86.3-100%</b>	--	--	
-Larger cell	25/25	100%	86.3-100%	--	--	
<b>High Grade:</b> <sup>7,10,12,11,14,16</sup>	<b>102/106</b>	<b>96%</b>		--	--	
-Small non-cleaved	4/4	100%	39.8-100%	--	--	
-Large immunoblastic	26/27	96%	81-99%	0/2	--	0-84.7%
-Large lymphoblastic (pre B)	1/1	100%	--	0/2	--	0-84.7%
-Malignant	71/74	96%	87-99%	--	--	
<b>Miscellaneous:</b> <sup>7,10,14,15,16,17,21,22</sup>	<b>21/21</b>	<b>95%</b>		--	--	
-Immunoblastic Sarcoma	2/2	100%	15.8-100%	--	--	
-Marginal Zone Lymphoma	1/1	100%	--	--	--	
-Sinonasal Large-Cell Lymphoma	0/1	--	--	--	--	
-Monocytoid Lymphoma	17/17	100%		--	--	
-T-cell Lymphoma				0/44	--	0-11.5%
-High Grade Lymphoblastic Lymphoma				0/1	--	
<b>Other Lymphoproliferative Disorders:</b> <sup>7,14,16,17</sup>	<b>74/94</b>	<b>79%</b>	<b>78-95%</b>	--	--	
-Hairy Cell Leukemia	40/46	87%	73-95%	--	--	
-Plasmacytoma/Plasma Cell Myeloma	1/11	10%	0.5-42%	--	--	
-Lymph nodules/Bone marrow biopsies <sup>27</sup>						
---Polycythemia Vera	4/4	100%	39.8-100%	--	--	
---Idiopathic Thrombocythaemia	7/7	100%	59-100%	--	--	
---Chronic Myeloid Leukemia	0/4	--	0-60.2%	--	--	
Myelofibrosis/ Osteomyelosclerosis	17/17	100%	80.5-100%	--	--	
---Borderline	5/5	100%	48-100%	--	--	

**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>9,10,13,19,20</sup>

TISSUE	NO. REACTIVE / NO. TESTED	%	95% CONFIDENCE INTERVAL
Lymphocyte Depleted	1/9	11%	0.3-48.2%
Lymphocyte Predominant	49/51	96%	86.5-98.9%
Mixed Cellularity	8/44	18%	8-30%
Nodular Sclerosing	2/33	6%	1-20.5%
Inconspicuous Nodularity	5/5	100%	48-100%
Diffuse	4/4	100%	39.8-100%
Interfollicular	0/1	----	
Unclassified	0/3	----	0-70.8%
<b>Total:</b>	69/150	46%	---

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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OCT - 3 1997

Food and Drug Administration  
2098 Gaither Road  
Rockville MD 20850

Stephen A. Tillson, Ph.D.  
Vice President Scientific Affairs/  
Quality Assurance  
VENTANA MEDICAL SYSTEMS, INC.  
3865 North Business Center Drive  
Tucson, Arizona 85705

Re: K973390  
Trade Name: ChemMate™ L26 (CD20)  
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.

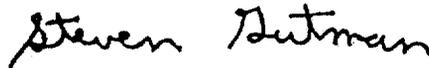
Page 2

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

510(k) Number (if known): K973390

Device Name: ChemMate L26(CD20)

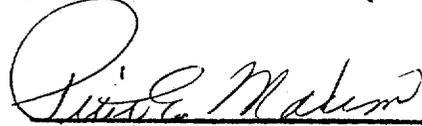
Antibody Reagent

**Indications For Use:**

To qualitative aid in the identification by light microscopy of human cells of B-cell lineage, by recognizing CD20 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 of B-cell origin and must be interpreted by a pathologist within the context of clinical data, gross and microscopic morphologic 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)



(Division Sign-Off)

Division of Clinical Laboratory Devices

510(k) Number

K973390

Prescription Use   
(Per 21 CFR 801.109)

OR

Over-The-Counter Use

(Optional Format 1-2-96)