

71-473343  
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## 510(k) SUMMARY

Date: September 22, 1997

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Registration # : 2028492

Trade Name: ChemMate™ LCA (CD45)

Class II

Intended Use: FOR IN VITRO DIAGNOSTIC USE.

ChemMate™ LCA (CD45; Clones PD7/26/16 and B11) is intended for laboratory use to qualitatively aid in the identification by light microscopy of human cells of lymphoid origin, by recognizing Leukocyte Common Antigen (LCA), in normal and pathological paraffin embedded tissues processed in interpreted by a pathologist within the context of clinical data, gross and microscopic morphological data and multiple chemical and immunohistochemical stains.

This mouse monoclonal antibody has been optimally prediluted for use with the ChemMate™ SDK605 and SDK305 Secondary Detection - Peroxidase/DAB kits. Additionally, the prediluted ChemMate™ LCA (CD45) antibody as well as Peroxidase/DAB kits have been optimized for use with the TechMate™ for automated immunohistochemical staining.

## 510K SUMMARY OF SAFETY AND EFFECTIVENESS

### SUMMARY AND EXPLANATION

The ChemMate™ LCA (CD45) is comprised of a mixture of two mouse monoclonal antibodies, clones PD7/26/16 and 2B11; each is of the IgG1 class of immunoglobulins.<sup>1</sup> Please refer to Warnke, et. al.<sup>1</sup> for a description of the cultivation, characterization and selection of these two clones. Each clone reacts with a different epitope of a family of membrane glycoproteins present on most human leukocytes known as the leukocyte common antigen (LCA). Tissues analyzed were either frozen or were embedded in paraffin and fixed with one of the following fixatives: formol saline, neutral buffered formalin, zinc sulfate [1%] formalin, B5, Bouin's, or acetic acid [2%] formol saline.<sup>1-3</sup> The LCA family consists of five to eight glycoproteins (molecular weight 180 to 220 kD)<sup>4-6,19</sup> The clone PD7/26/16, included in the Fourth International Workshop on Human Leukocyte Differentiation Antigens (Vienna, 1989), was confirmed to react with an epitope expressed on three of the glycoproteins in the LCA family (MW 190, 205, and 220 kD) and has been designated as CD45RB.<sup>5</sup> The clone 2B11, included in the Third International Workshop on Human Leukocyte Differentiation Antigens (Oxford, 1986), was confirmed to react with epitopes on four of the LCA glycoproteins (MW 180, 190, 205, and 220 kD).<sup>4</sup> For additional information of the CD45 isoforms, see Knapp, et al.<sup>5</sup>

A unique feature of the ChemMate™ LCA (CD45) is its ability to recognize epitopes on lymphocytes that survive the rigors of processing and fixation. The resultant advantage in the use of this antibody is its applicability with formalin-fixed specimens.<sup>1</sup> Excessive exposure of tissue to formalin beyond what is required for adequate fixation will result in increased cross linking and loss of many reactive epitopes. For example, in fresh (frozen) tissue, cross linking is eliminated hence antigenic reactivity is well preserved. It is in such frozen specimens that reactivity with the clones PD7/26/16 and 2B11 is not only demonstrated among lymphoid cell populations but may also be rarely demonstrated in some myeloid populations.<sup>3</sup>

In paraffin-embedded, fixed specimens, the strongest labeling is seen on lymphoid cells, where it is most intense on the cell surface and less marked within the cytoplasm. Weaker membranous and/ or cytoplasmic staining is seen on macrophages and histiocytes, while other myeloid cells variably demonstrate even weaker staining or are frequently unreactive.<sup>1,7</sup> ChemMate™ LCA (CD45) may be of value in assisting in the recognition of certain neoplasms, since neoplastic cells may, in a proportion of cases, fail to display the usual morphologic features of normal leukocytes in H & E sections, or may display atypical morphologic features.<sup>8-10</sup> Studies have also demonstrated LCA reactivity in many lymphomas and other hematopoietic neoplasms of lymphoid

type while neoplasms of epithelial, mesenchymal, or neural derivation remain unreactive.<sup>1,3,7,11</sup> The antibody is reactive with most, but not all neoplastic B and T cells in non-Hodgkin's lymphomas and leukemias of B and T cell type, malignant lymphoma of the thyroid, and hairy cells.<sup>7,12-16</sup> In a study of non-Hodgkin's lymphomas that compared genotypic analysis with immunophenotyping in paraffin-embedded tissue sections (fixed in B5 or 10% buffered formalin), LCA was positive in 42 of 44 cases (95%).<sup>24</sup> Rare Reed-Sternberg cells and their variants have been reported to reveal membrane staining for LCA, although most Reed-Sternberg cells appeared negative or indeterminate due to the presence of adjacent strongly LCA positive reactive lymphoid cells.<sup>7</sup> 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. A summary of immunoreactivity found in paraffin-embedded cells/tissues and neoplasms (from references 1 and 7) may be found in Tables I-V of Performance Characteristics in this insert.

The antibody has been nonreactive with most carcinomas and tissues of epithelial, mesenchymal, and neural origin, as well as malignant melanomas, rhabdomyosarcomas and Ewing's sarcoma<sup>1,7</sup>. These observations are also borne out in the immunoreactivity profiles of Table IV and V in this insert. It should however be noted that the interpretation of any positive LCA staining or its absence should be complemented by morphological studies and proper controls and should be evaluated within the context of the patient's clinical history and other diagnostic tests by a qualified individual.

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

1. In poorly fixed tissue specimens, nonspecific staining of non-lymphoid tissues may be observed, particularly epithelium and smooth muscle.
2. Association between lymphocytes and secretory ductal epithelium in the production of immunoglobulin is well known. LCA staining may be exhibited in the epithelium of both fibroadenoma and fibrocystic disease of the breast.<sup>20</sup> Although LCA reactivity has not been extensively studied in malignancies of the breast such as secretory carcinoma, signet ring cell lobular or ductal carcinoma, or for cystosarcoma phylloides, it is possible that LCA staining may also occur in some of these conditions. LCA reactions in breast tissues should not present differential difficulties in that histologic patterns in normal and abnormal breast tissues should be recognizable. Additionally, LCA is generally employed in a panel typically including cytokeratins and other markers (e.g., vimentin, S100).
3. It has been reported that the sensitivity of clones PD7/26/16 and 2B11 is 90-93% for non-Hodgkin's lymphomas. False negative results have been seen

in acute lymphoblastic leukemia.<sup>7,22,24</sup> It is recommended that a panel of antibodies be used to rule out lymphoid tumors.<sup>23</sup>

4. 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.
5. LCA positive lymphocytes closely apposed to carcinoma cells give the appearance of membrane reactivity to the latter cells<sup>7</sup>.
6. To avoid false positive interpretations, cytoplasmic staining unaccompanied by membrane staining should not be considered a positive result.

#### **Performance Characteristics:**

Reproducibility: ChemMate™ LCA (CD45), and Negative Control Reagent have been tested on serial sections of 271 tissue specimens (both normal and tumor specimens were included in the study; see Tables IB and V). Runs were performed a total of three times, with each run being performed on a different day. Consistent staining results were obtained.

Immunoreactivity: The following immunoreactivities have been demonstrated in paraffin-embedded tissues. The secondary staining systems were either ABC peroxidase or Indirect secondary antibody labeled peroxidase. The lists provided below (see Tables IA, II - IV) are not exhaustive but characterize the types of immunoreactivity reported in the literature for clones contained in the monoclonal antibody cocktail of ChemMate™ LCA (CD45). Tables IIB and V are summaries of the immunoreactivity studies performed by BioTek Solutions using ChemMate™ LCA (CD45) and the ChemMate™ Secondary Detection - Peroxidase/DAB Kit.

**TABLE IA**  
**REACTIVE AND NONREACTIVE NORMAL TISSUES/CELLS**<sup>1,7,17, 18, 21</sup>

REACTIVE CELLS	VARIABLY REACTIVE CELLS	NONREACTIVE CELLS
Follicular center lymphoid cells	Interfollicular transformed lymphoid cells immunoblasts)	Polymorphonuclear leukocytes, rare myeloid precursors with weak staining
Follicular mantle zones	Epithelioid histiocytes	Erythroid cells
Interfollicular small lymphocytes	Sinus histiocytes	Megakaryocytes
Perisinusoidal cells	Plasma cells	Tingible body macrophages with occasional small cytoplasmic granules
Splenic white pulp	Monocytes Macrophages	Interdigitating reticulum cells with rare, weak membrane staining
Splenic red pulp lymphoid cells		Splenic macrophages and sinus lining cells
Thymic lymphocytes		Thymic epithelial cells
Mast cells		Epithelium
Osteoclast		Langerhans' cells, skin Connective tissue

Table IA Note: A total of 45 tissues were fixed in either 10% neutral buffered formalin, B5, or Zenker's acetic acid solution. Three specimens were fixed in multiple fixatives (B5, Zenker's, formalin, and Bouin's). Tissues were embedded in paraffin, and the secondary staining systems were either ABC peroxidase or Indirect secondary antibody labeled peroxidase. The tissues evaluated included:

- |   |                                   |
|---|-----------------------------------|
| bone marrow [6]                                     | dermatopathic lymphadenitis [4]   |
| lymph nodes (nonspecific reactive hyperplasia) [10] | normal skin [2]                   |
| prostate (severe chronic prostatitis) [1]           |                                   |
| salivary gland (benign lymphoepithelial lesion) [1] | spleen (hyperplastic changes) [5] |
| sarcoidosis [5]                                     | thymus [3]                        |
| talc granuloma [1]                                  | toxoplasmic lymphadenitis [4]     |
| thyroid (Hashimoto's thyroiditis) [3]               |                                   |

**TABLE IB  
REACTIVE AND NONREACTIVE NORMAL TISSUES/CELLS**

<b>REACTIVE CELLS</b>	<b>VARIABLY REACTIVE CELLS</b>	<b>NONREACTIVE CELLS</b>
lymphocytes		adrenal glandular epithelium breast epithelium & stroma neurons glia squamous epithelium heart muscle colonic epithelium small intestinal epithelium renal epithelium hepatocytes / liver bile ducts alveolar epithelium striated muscle ovarian stroma & epithelium pancreatic epithelium prostate epithelium gastric epithelium testicular & interstitial epithelium thyroid epithelium uterine epithelium, muscle & stroma

**Table IB Note:** In studies performed by BioTek Solutions, a total of 126 normal tissues were fixed in 10% neutral buffered formalin, embedded in paraffin, immunostained with ChemMate™LCA-CD45 and the ChemMate™ Secondary Detection - Peroxidase/DAB Kit. All tissues were stained using the TechMate™ Automated Staining System. The tissues evaluated included:

adrenal [3]	skin [2]
brain [7]	small intestine [2]
breast [50]	spleen [3]
heart [3]	squamous epithelial [2]
kidney [5]	stomach [1]
large intestine [2]	striated muscle [2]
liver [5]	testis [5]
lung [5]	thyroid [6]
ovary [5]	tonsil [3]
pancreas [5]	uterus [5]
prostate[5]	

**TABLE II**  
**REACTIVE B- AND T- CELL NON-HODGKIN'S LYMPHOMA<sup>7</sup>**

	<b>NO. REACTIVE/ NO. TESTED</b>	<b>%</b>	<b>95% CONFIDENCE INTERVAL</b>
<b>A. TISSUE: B-CELL</b>			
Lymphoplasmacytic Follicular center cell	4/4	100%	39.8-100%
-small cleaved	15/15	100%	78.2-100%
-large cleaved	4/6	66.7%	22-95%
-mixed small and large	5/5	100%	48-100%
-small non-cleaved	5/5	100%	48-100%
-large non-cleaved	11/12	91.7%	62.5-99.7%
Immunoblastic sarcoma	14/14	100%	76.8-100%
<b>B. TISSUE: T-CELL</b>			
Mycosis fungoides	1/1	100%	---
Immunoblastic sarcoma	10/11	90.9%	58-99.5%
lymphoblastic	2/4	50%	9.0-91%
Unclassified	3/3	100%	29.2-100%

Table II Note: Confidence intervals were not calculated for those cases with a sample size of one. The reactivity however was included for anecdotal reference information.

A total of 80 specimens were fixed in either formalin (25 specimens), B5 (48 specimens), or Zenker's solution (2). Five specimens were fixed in multiple fixatives (B5, formalin, Zenker's, and Bouin's). The specimens were embedded in paraffin, and the secondary staining systems were either ABC peroxidase or indirect secondary antibody labeled peroxidase.

**TABLE III  
OTHER HEMATOPOIETIC NEOPLASMS <sup>7</sup>**

TISSUE /RELEVANT CELL TYPE	NO. REACTIVE/ NO. TESTED	%	95% CONFIDENCE INTERVAL
Chronic Lymphocytic Leukemia			
-B-cell Type: lymphoid cells	3/3	100%	29.2-100%
-T-cell Type: lymphoid cells	3/3	100%	29.2-100%
Acute Lymphoblastic Leukemia:			
-lymphoblasts	3/8	37.5%	8.5-75.5%
Prolymphocytic (B-cell) Leukemia:			
-prolymphocytes	1/1	100%	---
Hairy Cell Leukemia:			
-Hairy Cells	5/5	100%	48-100%
Acute Myelogenous Leukemia:			
- myeloid cells	0/7	0%	0-41%
Chronic Myelogenous Leukemia:			
- myeloblasts	0/2	0%	0-84.7%
Erythroleukemia:			
-erythroblasts	0/2	0%	0-84.7%
Monocytic Leukemia:			
-monoblasts	1/1	100%	---
Polycythemia Vera:			
-erythroid cells	0/2	0%	0-84.7%
Extramedullary Hematopoiesis:			
-myeloid cells	0/3	0%	0-70.8%
-megakaryocytes	0/3	0%	0-70.8%
Multiple Myeloma:			
-plasma cells	10/10	100%	68.5-100%
Plasma Cell Leukemia:			
-plasma cells	0/1	0%	---
Systemic Mast Cell Disease:			
-mast cells	3/3	100%	29.2-100%

Table III Note: Confidence intervals were not calculated for those cases with a sample size of one. The reactivity however was included for anecdotal reference information.

A total of 51 specimens were fixed in either formalin (2 spleens, 1 lymph node, and 1 skin specimen), B5 (9 spleens, 5 lymph nodes, and 1 soft tissue mass), or Zenker's acetic acid solution (32 bone marrow specimens). The specimens were embedded in paraffin, and the secondary staining systems were either ABC peroxidase or indirect secondary antibody labeled peroxidase.

**TABLE IV**  
**NONREACTIVE NON-LYMPHOID PATHOLOGICAL TISSUES** <sup>1,7</sup>

TISSUE	NO. NONREACTIVE/ NO. TESTED	%	95% CONFIDENCE INTERVAL
Squamous cell carcinoma	4/4	100%	39.8-100%
Nasopharyngeal squamous cell carcinoma	1/1	100%	---
Adenocarcinoma	54/54	100%	93-100%
Ovarian serous cystadenocarcinoma	1/1	100%	---
Transitional cell carcinoma	2/2	100%	15.8-100%
Bladder-invasive transitional cell carcinoma	1/1	100%	---
Metastatic carcinoma	5/5	100%	48-100%
Basal-cell carcinoma	1/1	100%	---
Breast-infiltrating lobular carcinoma	2/2	100%	15.8-100%
Small cell anaplastic lung carcinoma	10/10	100%	68.5-100%
Breast-infiltrating ductal carcinoma	2/2	100%	15.8-100%
Pulmonary large-cell undiff. carcinoma	1/1	100%	---
Pulmonary small-cell undiff. carcinoma	2/2	100%	15.8-100%
Nasopharyngeal undiff. carcinoma	7/7	100%	59-100%
Laryngeal undiff. carcinoma	1/1	100%	---
Medullary carcinoma, thyroid	1/1	100%	---
Thymoma (epithelial)	4/4	100%	39.8-100%
Amelanocytic malignant melanoma	5/5	100%	48-100%
Malignant melanoma	3/3	100%	29.2-100%
Alveolar rhabdomyosarcoma	3/3	100%	29.2-100%
Ewing's sarcoma	9/9	100%	66-100%
Neuroblastoma	2/2	100%	15.8-100%
Soft-tissue fibrosarcoma	1/1	100%	---
Soft-tissue malignant fibrous histiocytoma	4/4	100%	39.8-100%
Eosinophilic granuloma	1/1	100%	---
Granular cell tumor	1/1	100%	---
Adrenal Pheochromocytoma	2/2	100%	15.8-100%
Adrenal neuroblastoma	3/3	100%	29.2-100%
Glioblastoma	1/1	100%	---
Neurofibroma/neuroma	6/6	100%	54.1-100%
Oligodendroglioma	1/1	100%	---
Cerebellar astrocytoma	1/1	100%	---
Meningioma	1/1	100%	---
Chordoma	1/1	100%	---
Skeletal giant cell tumor	1/1	100%	---
Carcinoid, lung	1/1	100%	---
Ileal carcinoid tumor	2/2	100%	15.8-100%
Colonic carcinoid carcinoma	1/1	100%	---
Wilm's tumor	1/1	100%	---
Germ cell tumor	7/7	100%	59-100%
Medulloblastoma	1/1	100%	---
Ependymoma	1/1	100%	---
Testicular embryonal carcinoma	1/1	100%	---
Testicular spermatocytic seminoma	1/1	100%	---
Testicular seminoma	1/1	100%	---

Table IV Note: Confidence intervals were not calculated for those cases with a sample size of one. The reactivity however was included for anecdotal reference information.

A total of 162 tissues were fixed in either formol saline, neutral buffered formalin, 10% neutral buffered formalin, B5, Zenker's acetic acid solution, acetic acid (2%) formol saline, or Bouin's. Six specimens were fixed in multiple fixatives (B5, Zenker's, formalin, and Bouin's). Tissues were embedded in paraffin, and the secondary staining systems were either ABC peroxidase or indirect secondary antibody labeled peroxidase.

**TABLE V  
REACTIVE AND NONREACTIVE PATHOLOGICAL TISSUES/CELLS**

<b>REACTIVE CELLS</b>	<b>VARIABLY REACTIVE CELLS</b>	<b>NONREACTIVE CELLS</b>
lymphoma cells		breast epithelium & stroma carcinoid epithelium colonic carcinoma gastric carcinoma hepatocellular carcinoma lung carcinoma ovarian carcinoma prostatic carcinoma thyroid carcinoma endodermal sinus carcinoma melanocytes placental trophoblasts Ewing's sarcoma fibrosarcoma seminoma seminiferous epithelium teratoma epithelia & mesenchyme

Table V Note: In studies performed by BioTek Solutions, a total of 145 pathological tissues were fixed in 10% neutral buffered formalin, embedded in paraffin, immunostained with ChemMate™ LCA-CD45 and the ChemMate™ Secondary Detection - Peroxidase/DAB Kit. All tissues were stained using the TechMate™ Automated Staining System. The tissues evaluated included:

- |                              |                                |
|------------------------------|--------------------------------|
| breast carcinoma [65]        | thyroid carcinoma [1]          |
| lymphoma [45]                | endodermal sinus carcinoma [1] |
| carcinoid [4]                | melanoma [6]                   |
| colonic carcinoma [3]        | placental tumor [1]            |
| gastric carcinoma [2]        | sarcoma, Ewing's [1]           |
| hepatocellular carcinoma [3] | sarcoma, fibro [1]             |
| lung carcinoma [2]           | seminoma [2]                   |
| ovarian carcinoma [1]        | teratoma [1]                   |
| prostatic carcinoma [6]      |                                |

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Re: K973393  
Trade Name: ChemMate™ LCA (CD45)  
Regulatory Class: II  
Product Code: DEH  
Dated: June 27, 1997  
Received: July 1, 1997

SEP 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 (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.

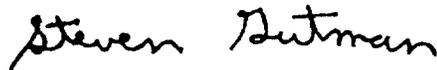
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Under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88), this device may require a CLIA complexity categorization. To determine if it does, you should contact the Centers for Disease Control and Prevention (CDC) at (770)488-7655.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. 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): K 973393

Device Name: LCA (leukocyte common antigen) ChemMate: includes ChemMate secondary detection kits peroxidase DAB SDK 605 & 305; ChemMate Negative Control reagent; ChemMate standard secondary buffer kit

**Indications For Use:**

For the LCA primary antibody reagent:

To qualitatively aid in the identification by light microscopy of human cells of lymphoid origin, by recognizing Leukocyte Common Antigen (LCA) in normal and pathologic paraffin embedded tissues processed in neutral buffered formalin, B5, or Bouin's fixative.

For the Ancillary Reagents:

To aid in the performance of immunohistochemical tests

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

*Peter E. Mafon*

(Division Sign-Off)

Division of Clinical Laboratory Devices

510(k) Number K 973393

Prescription Use   
(Per 21 CFR 801.109)

OR

Over-The-Counter Use

(Optional Format 1-2-96)