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K971905

510(k) Summary

Submitter: DAKO Corporation  
6392 Via Real  
Carpinteria, CA 93013  
805-566-6655

DEC 12 1997

Contact: Gretchen M. Murray, Ph.D.

Date Summary Prepared: December 4, 1997

Device Name: 1) DAKO<sup>®</sup> Mouse Anti-Human Cytokeratin, High Molecular Weight, Clone 34βE12. Monoclonal Antibody for Immunoenzymatic Staining (Product Code No. M0630)  
2) DAKO<sup>®</sup> Ready-to-Use Mouse Anti-Human Cytokeratin, High Molecular Weight, Clone 34βE12, Monoclonal Antibody and Negative Control Reagent for Immunoenzymatic Staining (Product Code No. N1553)

Device Classification: Class I or 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: Becton Dickinson Anti-Human Cytokeratin, CAM5.2 (FDA K864893).

Device Description: 1) Monoclonal Mouse Anti-Human Cytokeratin, High Molecular Weight, clone 34βE12 (Product Code No. M0630) is a mouse anti-human antibody produced as a tissue culture supernatant. The antibody is supplied in 0.05M Tris-HCl buffer, pH 7.2, containing fetal calf serum and 15mM sodium azide. (1mL total volume).

2) Ready-to-Use Monoclonal Mouse Anti-Human Cytokeratin, High Molecular Weight, clone 34βE12 Antibody and Negative Control (Product Code No. N1553) 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 fetal calf serum and 15mM 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 and 15mM sodium azide (5mL total volume).

Intended Use: For *In Vitro* Diagnostic Use

Monoclonal mouse anti-human Cytokeratin, High Molecular Weight, clone 34βE12 (34βE12) is intended for laboratory use to qualitatively identify by light microscopy the 66, 57, 51 and 49kD<sup>3</sup> proteins corresponding to cytokeratins 1, 5, 10 and 14 of the Moll catalog in acetone or methanol fixed, frozen and formalin,

methacarn or Carnoy's fixed, paraffin embedded tissues. 34βE12 specifically binds to antigens located in the cytoplasm of normal squamous and ductal epithelial cells. Positive results aid in the classification of normal and abnormal cells and tissues and serve as an adjunct to conventional histopathology. 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.

Indicated Use:

Anti-Human Cytokeratin, High Molecular Weight, Clone 34βE12 Antibody may be used as one member of a panel of antibodies to aid in the differential diagnosis of anaplastic cells of undetermined origin. When used with markers of simple epithelium, it can aid in the differentiation of carcinomas from non epithelial tumors, e.g., gliomas, lymphomas, melanomas, sarcomas or seminomas. Because it does not react with all carcinomas, it may be used also as an aid in the subclassification of carcinomas. It is also useful in the differential diagnosis of small-acinar lesions of the prostate gland because it stains basal cells which are absent in the disease.

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. All tissues were formalin fixed and paraffin embedded. Staining was performed using the DAKO LSAB®2 Peroxidase kit system (Code No. K0677).

Normal tissues exhibiting positive staining with 34βE12 included the following: breast, cervix, esophagus, prostate, salivary gland, skin, thymus and tonsil. Normal tissues that did not stain with 34βE12 include adrenal, bone marrow, brain (cerebellum and cerebrum), colon, heart, kidney, liver, lung, mesothelial cells, ovary, pancreas, parathyroid, pericardium, peripheral nerve, pituitary, skeletal muscle, small intestine, spleen, stomach, testis, thyroid and uterus.

Reproducibility Testing:

Eight serial sections from each of three different formalin-fixed, paraffin embedded blocks of normal skin 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® Mouse Anti-Human Cytokeratin clone 34βE12 (Code No. N1553). 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 34βE12 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. (See Section 3 for the Report of the Results of the Reproducibility Testing)

Published Immunoreactivity:

Fifteen articles published on the characterization or clinical use of high molecular weight cytokeratin were used in the submission. Eleven of those articles reported on studies using 34βE12. Following is a brief summary of the compiled information.

Cytokeratins are intermediate filament cytoskeletal proteins essential to development and differentiation of epithelial cells. Approximately twenty different cytokeratins have been identified and are classified and numbered according to molecular weight and isoelectric points.<sup>1</sup> In general, most low molecular weight cytokeratins (40kD-54kD) are distributed in nonsquamous epithelium, Moll's Catalog numbers 7-8 and/or 17-20.<sup>2</sup> High molecular weight cytokeratins (48kD-67kD) are found in the upper portions of the epidermis and squamous epithelium, Moll's Catalog numbers 1-6 and/or 9-16.<sup>2</sup> The DAKO® Mouse Anti-Human Cytokeratin, High Molecular Weight, clone 34βE12 antibody has been shown to react with the 66, 57, 51 and 49kD proteins corresponding to cytokeratins 1, 5, 10 and 14 of the Moll Catalog.<sup>1,3,4</sup> Positive immunoreactivity with the 66, 57, 51 and 49kD antigen appears as diffuse cytoplasmic staining and indicates cells of epithelial nature, specifically squamous or ductal epithelium.<sup>5</sup>

34βE12 reacts with a variety of normal epithelial tissue including: squamous epithelium and sweat ducts in skin,<sup>4</sup> all epithelial layers including luminal and basal epithelium and ductal cells in breast,<sup>6</sup> some pneumocytes, mesothelium and bronchial epithelium in lung, collecting duct epithelia in kidney and ductal cells in the pancreas, bile ducts in the liver, and mesothelium and a portion of epithelium (cells with a more basal location ) of the gastrointestinal tract.<sup>4</sup> Hepatocytes, pancreatic acinar cells, proximal renal tubules, and nonepithelial normal tissues are not labeled by 34βE12.<sup>4</sup>

Monoclonal antibodies to intermediate filaments can be used as an aid in the histologic subclassification of human neoplasms. The cytoskeletal phenotype of most tumors resembles that of their normal cellular counterpart regardless of the degree of differentiation. Thus, they can be used as an aid in the differential diagnosis of anaplastic tumors of unknown origin.<sup>5</sup>

It has been reported<sup>5,6</sup> that the 34βE12 antibody reacted positively with high molecular weight cytokeratins present in squamous cell and ductal or transitional cell carcinomas including: squamous cell carcinoma of the skin, lung and nasopharynx, ductal carcinoma of the breast, pancreas, bile duct and salivary gland as well as transitional cell carcinomas of the bladder and nasopharynx and thymomas. 34βE12-negative epithelial tumors are either "acinar" type adenomas (e.g., pituitary) or adenocarcinomas of simple epithelia (e.g., endometrial carcinomas, renal and hepatocellular carcinomas) or neuroendocrine tumors.<sup>4,5,7</sup> 34βE12 stained epithelial mesotheliomas, but failed to react with sarcomatoid or desmoplastic mesotheliomas.<sup>8</sup> Thus, 34βE12 may be used as an aid in the subclassification of carcinomas.<sup>5</sup>

Even though clone 34βE12 was negative with most non epithelial tumors e.g., gliomas, lymphomas, melanomas, sarcomas or seminomas,<sup>4,5,9</sup> it cannot be used as the sole epithelial marker in the differential diagnosis of carcinomas from non epithelial tumors. Because it does not react with all carcinomas, another marker for simple epithelium must be incorporated into a panel of antibodies with 34βE12 to aid in the differential diagnosis of anaplastic tumors of unknown origin. Epitheloid sarcomas and synovial sarcomas, however, have shown to exhibit positive staining with various cytokeratin antibodies including 34βE12.<sup>5,10</sup>

It has been suggested also that 34 $\beta$ E12 is useful in the differential diagnosis of small acinar lesions of the prostate gland.<sup>11</sup> It was proposed that its diagnostic value lies in the identification of basal cells. O'Malley, et. al. saw positive staining of basal cells in 47 examples of benign prostatic lesions including atypical adenomatous hyperplasia (13), basal cell hyperplasia (11), atrophy (16), post-sclerotic hyperplasia (5) and fibroepithelial nodule (2), while 21 cases of small-acinar adenocarcinomas showed no reactivity with the antibody. This was explained as loss of basal cells in this condition. It was stressed that loss of basal cell layer is not uniform in all prostatic adenocarcinomas. Basal cells are lost only in small-acinar adenocarcinomas. It was recommended that complete absence of staining of prostate lesions with 34 $\beta$ E12 should be regarded as very suggestive, but not diagnostic of malignancy.

Shah et. al.,<sup>12</sup> suggested clinical usefulness of 34 $\beta$ E12 as an aid in the differentiation of Paget's disease and Bowen's disease (carcinoma in situ) from Pagetoid superficial spreading melanoma. 34 $\beta$ E12 positivity was reported in Paget's disease of the breast (5/5) and Bowen's disease (10/10). However only 1/4 of Paget's disease of the vulva stained. None of 6 of the Pagetoid superficial spreading melanomas stained.

#### Bibliography:

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Gretchen M. Murray, Ph.D.  
Assistant Manager, Regulatory Affairs  
DAKO Corporation  
6392 Via Real  
Carpinteria, California 93013

Food and Drug Administration  
2098 Gaither Road  
Rockville MD 20850

DEC 12 1997

Re: K971905/S1

Trade Name: 1.) DAKO® Mouse Anti-Human Cytokeratin, High  
Molecular Weight, Clone 34βE12, Monoclonal Antibody for  
Immunoenzymatic Staining (Product Code No. M0630).  
2.) DAKO® Ready-to-Use Mouse Anti-Human Cytokeratin, High  
Molecular Weight, Clone 34βE12, Monoclonal Antibody and  
Negative Control Reagent for Immunoenzymatic Staining  
(Product Code No. N1553)

Regulatory Class: II Product Code: DEH

Dated: September 10, 1997

Received: September 15, 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 (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.

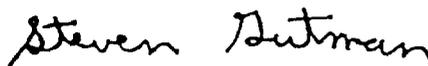
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Under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88), this device may require a CLIA complexity categorization. To determine if it does, you should contact the Centers for Disease Control and Prevention (CDC) at (770)488-7655.

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

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Device Description: 1) Monoclonal Mouse Anti-Human Cytokeratin, High Molecular Weight, clone 34βE12 (Product Code No. M0630) is a mouse anti-human antibody produced as a tissue culture supernatant. The antibody is supplied in 0.05M Tris-HCl buffer, pH 7.2, containing fetal calf serum and 15mM sodium azide. (1mL total volume).

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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. All tissues were formalin fixed and paraffin embedded. Staining was performed using the DAKO LSAB®2 Peroxidase kit system (Code No. K0677).

Normal tissues exhibiting positive staining with 34βE12 included the following: breast, cervix, esophagus, prostate, salivary gland, skin, thymus and tonsil. Normal tissues that did not stain with 34βE12 include adrenal, bone marrow, brain (cerebellum and cerebrum), colon, heart, kidney, liver, lung, mesothelial cells, ovary, pancreas, parathyroid, pericardium, peripheral nerve, pituitary, skeletal muscle, small intestine, spleen, stomach, testis, thyroid and uterus.

Reproducibility Testing:

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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® Mouse Anti-Human Cytokeratin clone 34βE12 (Code No. N1553). Concurrently, one slide from each block was stained with the supplied negative control reagent.

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Public Health Service

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Assistant Manager, Regulatory Affairs  
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(Product Code No. N1553)

Regulatory Class: II Product Code: DEH

Dated: September 10, 1997

Received: September 15, 1997

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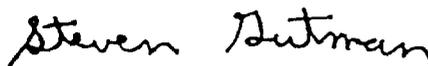
Page 2

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): K971905

Device Name: Monoclonal Mouse Anti-Human Cytokeratin, High Molecular Weight, clone 34βE12 Antibody for Immunoenzymatic Staining

Monoclonal Mouse Anti-Human Cytokeratin, High Molecular Weight, clone 34βE12 Ready-to-Use Antibody and Negative Control for Immunoenzymatic Staining

**Indications For Use:**

Monoclonal Mouse Anti-Human Cytokeratin, High Molecular Weight, Clone 34βE12 Antibody may be used as one member of a panel of antibodies to aid in the differential diagnosis of anaplastic cells of undetermined origin. When used with markers of simple epithelium, it can aid in the differentiation of carcinomas from non epithelial tumors, e.g., gliomas, lymphomas, melanomas, sarcomas or seminomas. Because it does not react with all carcinomas, it may be used also as an aid in the subclassification of carcinomas. It is also useful in the differential diagnosis of small-acinar lesions of the prostate gland because it stains basal cells which are absent in this disease.

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.

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

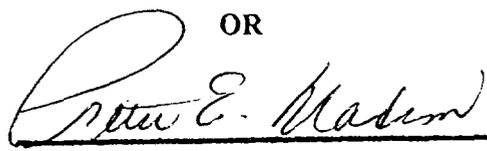
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Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use   
(Per 21 CFR 801.109)

OR

Over-The-Counter Use

IVD Use   
(Per 21 CFR 801.119)

  
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(Division Sign-Off)  
Division of Clinical Laboratory Devices  
510(k) Number K971905 (Optional Format 1-2-96)