MAR - 3 2000

K993957

## 510(k) Summary

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| Submitter: | DAKO Corporation<br>6392 Via Real<br>Carpinteria, CA 93013<br>805-566-6655 |
| Contact: | Gretchen M. Murray, Ph.D., Regulatory Affairs Manager |
| Date Summary Prepared: | October 30, 1999 (amended March 2, 2000) |
| Device Name: | 1) DAKO® Monoclonal Mouse Anti-Human Estrogen Receptor, Clone 1D5, Antibody for Immunoenzymatic Staining (Product Code No. M7047)<br><br>2) DAKO® Monoclonal Mouse Anti-Human Estrogen Receptor, Clone 1D5, Ready-to-Use Antibody and Negative Control Reagent for Immunoenzymatic Staining (Product Code No.N1575) |
| Device Classification: | Class II for prognostic immunohistochemical staining reagents (21 CFR 864.1860). |
| Panel: | Hematology and Pathology Devices Panel,<br>Division of Clinical Laboratory Devices. |
| Predicate Device: | Abbott ER-ICA Monoclonal, Clone H222 approved by the FDA as PMA # P880026 and downclassified to class II by 21 CFR 864.1860, Immunohistochemistry Reagents and Kits on June 3, 1998. Device package insert from this product is included in Section 2 of this submission. |

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| Device (Product) Description: | 1) Monoclonal Mouse Anti-Human Estrogen Receptor, Clone 1D5, Code No. M7047) is a mouse anti-human monoclonal antibody produced as a tissue culture supernatant. The antibody is supplied in 0.05M Tris-HCl buffer, pH 7.2, containing fetal bovine serum and 15mM sodium azide. (1mL total volume).<br><br>2) Monoclonal Mouse Anti-Human Estrogen Receptor, Clone 1D5 Ready-to-Use Antibody and Negative Control (Product Code No. N1575) 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 bovine serum and 15mM sodium azide (7mL total volume). The primary antibody is packaged with a negative control reagent consisting of a cocktail of purified mouse immunoglobulins ($IgG_1$, $IgG_{2a}$, $IgG_{2b}$, $IgG_3$ and IgM) in 0.05M Tris-HCl buffer, pH 7.6 and 15mM sodium azide (5mL total volume). |
| Intended Use: | For *In Vitro* Diagnostic Use<br><br>Monoclonal Mouse Anti-Human Estrogen Receptor, Clone 1D5 may be used in the semiquantitative detection of human estrogen receptor in tissue sections of human breast cancer by immunohistochemistry. The information gained by this assay can aid in assessing the likelihood of response to therapy as well as in the prognosis and management of breast cancer patients. |

**Statement of Substantial Equivalence:**

DAKO® Monoclonal Mouse Anti-Human Estrogen Receptor, 1D5 (anti-ER, 1D5) is a monoclonal antibody produced as a tissue culture supernatant which is available as a concentrate (Code No. M7047) and a prediluted primary (Code No. N1575).

Anti-ER, 1D5 immunohistochemically demonstrates the presence of estrogen receptor in a variety of normal and pathological tissues. In normal tissue, anti-ER, 1D5 labels estrogen containing cells. Pathological reactivity includes detection of estrogen receptor in breast cancer.

Anti-ER, 1D5 is comparable in use and technology to Abbott ER-ICA Monoclonal, clone H222 which labels cells in tissues and is currently in commercial distribution. Similarities of the anti-ER, 1D5 to the Abbott ER-ICA include that both products are monoclonal antibodies directed against the human Estrogen Receptor (ER). The differences between the two products include that the DAKO anti-ER, 1D5 is directed to the N-terminal end of the ER, while the H222 clone from the Abbott ER-ICA is directed against the functional section of the ER, coded for in exon 5 of the ER DNA. Clone H222 is of rat origin, while anti-ER, 1D5 is of mouse origin. Functionally, anti-ER, 1D5 reacts with an epitope exposed in formalin-fixed, paraffin-embedded tissues by heat induced epitope retrieval. The H222 clone binds to ER found in frozen tissues. When the H222 clone has been tested on formalin-fixed, paraffin-embedded tissues, the specificity was decreased from that seen with frozen tissues.

Visualization of the primary antibody for the Abbott ER-ICA is achieved using an indirect peroxidase anti-peroxidase (PAP) system. ER-ICA monoclonal is located by a goat anti-rat bridging antibody. Anti-Rat PAP complex is added, which recognizes the bridging antibody. Then a precipitating enzyme generated product (hydrogen peroxide) and a chromogen substrate solution, containing DAB are added. The reaction product produces a reddish brown precipitate at the locations of the primary antibody.

The DAKO anti-estrogen receptor, clone 1D5 is substantially equivalent to the Abbott ER-ICA Monoclonal, clone H222 in that both products specifically bind to estrogen receptor proteins located in the nuclei of cells. Both products require similar detection chemistry principles for visualization of the product, and both aid in the prognosis of breast carcinoma.

Functional comparison testing of anti-ER, 1D5 on formalin-fixed paraffin-embedded specimens and Abbott's ER-ICA using frozen breast cancer specimens is presented in Table 1.

I. Experimental Data

Normal Tissue Testing:
(The negative reagent control for these 2 studies was fetal bovine serum diluted with the same Tris-HCl buffer with 0.015M $NaN_3$ as the primary antibody.)

The required panel of normal tissues was tested with this antibody as specified in the 6/3/98 final version 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. K0672).

Normal tissues exhibiting positive staining with anti-ER, 1D5 included the following: breast, cervix and uterus. Refer to the package insert Table 2, Normal Tissue Reactivity for additional testing results or to Section 3 of this submission for the Report of the Results of the Normal Tissue Reactivity Testing.

Reproducibility Testing:

Eight serial sections from each of three different paraffin embedded blocks of human breast carcinoma 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 Monoclonal Mouse Anti-Human Estrogen Receptor, Clone 1D5 Ready-to-Use Antibody and negative control reagent consisting of fetal bovine serum in the equivalent diluent. 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 anti-ER, 1D5 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.)

II. Published Immunoreactivity

Twenty-six articles published on the characterization or clinical use of estrogen receptor were used in the submission. Twenty-three of those articles reported on studies using anti-ER, 1D5. Following is a brief summary of the compiled information.

Estrogen Receptor Characteristics

Steroid receptors exhibit a high affinity and specificity for their ligands. The human estrogen receptor (ER) is a dimeric protein of 65 kDa located primarily on the membrane of cell nuclei and belongs to a class of *trans*-acting proteins which stimulate transcription by binding to specific DNA elements, also known as hormone response elements. Through binding estrogen, the ER is induced to precisely stimulate gene transcription, hence is also known as an inducible enhancer factor. [1]

Measurement of the ER has been shown to be important in the initial evaluation of breast cancer patients, for providing information on the likelihood of a successful endocrine response and for the management of the patient and the tumor. [2, 3]

Development of ER-1D5 monoclonal antibody

The monoclonal antibody, anti-ER, 1D5 was produced in BALB/c mice by i.p. injection of recombinant estrogen receptor (RER). [4] The RER used was obtained by inserting human ER

cDNA into the NdeI-BamHI site of translation vector pETIIa and introducing the same into the 5' end of the coding sequence of ER, a fragment of the plasmid pSG5-HGO. This modified cDNA was then inserted into the plasmid expression vector pETIIa. *E. coli*, transformed with pETII-HGO, and produced a protein with molecular mass of 67kD. Clone 1D5 was shown to react with an epitope located in the N-terminal domain of ER.

Clone 1D5 Positivity in Normal Tissues

In normal frozen and formalin-fixed, paraffin-embedded human tissue, anti-ER, 1D5 reacts with the nuclei of cells known to contain large amounts of ER, including cells of the mammary gland and the uterus. No reactivity was found in tissues normally considered negative for ER. [4] When present, weak cytoplasmic staining was considered nonspecific.

Clone 1D5 Presence in Abnormal Tissues

In pathological tissues, anti-ER, 1D5 was examined for specificity and sensitivity for breast cancer as well as for the evaluation of patients for endocrine therapy. Numerous studies of cases of breast cancer showed anti-ER, 1D5 to be safe and effective in this endeavor. [5-13] On frozen tissues, anti-ER, 1D5 immunoreacted with 63/93 (67.7%) cases of breast cancer and only 1/30 (3.3%) nonbreast cancers reacted positively. [4] Direct comparison of anti-ER, 1D5 on formalin-fixed, paraffin-embedded (FFPE) specimens with H222 on frozen sections of the same tumors has been completed by 7 different laboratories on more than 1000 specimens. The results are reported in Table 1.

The specificity of anti-ER, 1D5 (either assessed as compared to H222 or to outcome with tamoxifen) varied from 51% to 79% while sensitivity varied from 89% to 100%. H222 was reported to be less sensitive but more specific in one article. [14] Thus, the use of IHC with anti-ER, 1D5 correlates well with a previously approved immunocytochemical assay for ER. However, clinical follow-ups have shown that IHC by use of anti-ER, 1D5 provided

Definition of positive IHC assay results with anti-ER, 1D5 have ranged somewhat arbitrarily from a minimum of any cells staining positive, to 5% of stained tumor nuclei, [21] to 10% [6, 11,13,15, 18 22] or 20%.[18] In over 900 cases of breast cancer, one investigator observed a strong relationship between staining intensity and the number of positive cells ($p$ 0.001).[9] Because of the above arbitrary limits of positivity, these authors and others [4, 20, 22-26] designed a semiquantitative "score" from the percentage of stained cells and the nuclear staining intensity (e.g. 0-3 or negative, weak, moderate, and strong). This scoring system is adopted for anti-ER, 1D5. However, Pertchuck et al (1996) found little support for the use of such scores.[13]

Image analysis systems [7,8,19] and automated stainers [5] were used in an effort to obtain greater objectivity in assessing positive expressions but have yet to be validated in the literature.

In 105 cases of node-negative primary breast cancer, anti-ER,1D5-positivity made no significant difference in predicting overall survival, whereas in 152 node-positive cases, anti-ER, 1D5-positivity was found to be prognostically relevant for predicting overall survival and predicting relapse-free survival.[11] Staining with anti-ER, 1D5 provided predictive information for the selection of patients who may benefit by hormonal treatment.[11] Image analysis of stained tissues from 250 cases of breast cancer showed disease progression to be 1.7 times and death rate to be 2.5 times higher in anti-ER, 1D5-negative cases than in 1D5-positive cases if the cut-off value was "optimally" selected. [5] Of 36 Anti-ER, 1D5-positive cases, 23 (64%) showed favorable responses to therapy, whereas 35/38 (92%) 1D5-negative cases showed disease progression.[13] Others [10] have reported that 1D5-positivity was a strong predictor of favorable primary response to tamoxifen in 89% of 72 cases and that treatment did not impede the detection of ER by anti-ER, 1D5.

Bibliography:


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TABLE 1

Table 1:

| Author/Journal | Study comparison | Number of samples | Scoring system | 2x2 H222 + - | | | Relationship to outcome |
|---|---|---|---|---|---|---|---|
| Mauri, et al. Appl Immunohistochem 2(3) 1994; 157[15] | 1D5 (DAKO) to H222 (frozen) | 374 | All cells with stained nuclei were counted as positive. 7.2% (1D5+/H222-) and 3.5% 1D5-/H222+. | 231 + 231<br>1D5 - 13<br>Total 244 | 27<br>103<br>130 | 258<br>116<br>374 | Specificity = 103/130 = 79.23<br>Sensitivity = 231/244 = 94.67 |
| Goulding, et al. Human Pathol 1995; 26:291[14] | 1D5 (DAKO ) paraffin to H222, frozen | 90 | H scores 1D5 correlation with H222 frozen R= 0.7, with p<0.0001. Same correlation with H222 paraffin | | | | H score of 50 = cut-off. ER 1D5 correlated with outcome to TAM 1D5 is more sensitive (90%vs 67%) but less specific (51% vs 62%) to H222 |
| Nedergaard et al. APMIS 1995; 103:20[18] | 1D5 (DAKO) to ER-ICA frozen and 1D5 to ER-ICA paraffin | 83 | | 1D5+53<br>- 2<br>Total 55 | 7<br>21<br>28 | 60<br>23<br>83 | Weak staining, more than 10% c cells corresponds to <100 fmol/mg<br><br>Specificity = 0.75, sensitivity = 0.96 |
| Pertschuk et al. Cancer 1996; 77: 2514[13] | 1D5 (DAKO) to ER-ICA frozen | 74 | Cut-off between positive and negative was at least 10% of tumor cells staining positive | 1D5+29<br>- 14<br>Total 43 | 7<br>24<br>31 | 36<br>38<br>74 | All had Stage IV disease.<br>Demographics<br>White 38<br>AfroAm 31<br>Hispanic 4<br>Asian 1<br><br>54 received tamoxifen ± adjuvar therapy<br><br>of 21 discordant cases, ER-1D5 correctly predicted endocrine response in 16 cases (p<0.02) |

| Author/Journal | Study comparison | Number of samples | Scoring system | 2x2<br>H222<br>+ - | Relationship to outcome |
|---|---|---|---|---|---|
| | | | | | 1D5 specificity = 25/48 (73%)<br>sensitivity = 23/26 (89%)<br>+ Predictive value = 23/36 (64%)<br>- Predictive value = 35/38 (92%)<br><br>In all cases better than H222 and ER by DCC |
| Leong and Milos. Appl. Immunohistochem 1993;1: 282[20] | ER 1D5 (DAKO) to H222 frozen | 31 | No negative ER specimens were evaluated. 1D5 correlated well with H222 on levels of positivity | | |
| Pellicer and Sundblad, Appl. Immunohistochem 1994;2: 141[12] | 1D5 (AMAC) to H222 | 300 patients with 5 year follow-up | Staining graded 0 – 3+ according to the nuclear staining intensity | + 137 53 190<br>1D5 - 12 98 110<br>149 (49.7%) 151 (50.3%) 300 | 1D5 was significant for DFS (p = 0.01) as well as OS (p=0.01). When staining intensity was stratified, OS reached (p= 0.007) and DFS reached (p= 0.003) for 3+ intensity<br><br>Specificity = 98/151 = 64.90%<br>Sensitivity = 137/149 = 91.95% |
| Hopkins et al. Am J Clin Path 1995;103: 503[17] | ER 1D5 to H222 paraffin and H222 frozen | 51 | | | Discrepant results occurred with weak or heterogeneous staining. 1D5 had 100%sensitivity and 88% specificity with H222 frozen |

| Author/Journal | Study comparison | Number of samples | Scoring system | 2x2<br>DCC<br>+ - | Relationship to outcome |
|---|---|---|---|---|---|
| Hendricks and Wilkinson Modern Path 1993; 6: 765[19] | H222 with proteolytic digestion of FFPE, 1D5 (AMAC) with HIER: Both were compared to DCC | 20 | | ER ICA + 8 1<br>6 5<br><br>ER 1D5 + 13 1<br>3 3 | ER 1D5 sensitivity = 93%<br>Specificity = 50%<br>+ predictive value = 81%<br>- predictive value = 75%<br><br>ER-ICA sensitivity = 57%<br>Specificity = 83%<br>+ predictive value = 89%<br>- predictive value = 45% |

**Statement of Substantial Equivalence:**

DAKO® Monoclonal Mouse Anti-Human Estrogen Receptor, 1D5 (anti-ER, 1D5) is a monoclonal antibody produced as a tissue culture supernatant which is available as a concentrate (Code No. M7047) and a prediluted primary (Code No. N1575).

Anti-ER, 1D5 immunohistochemically demonstrates the presence of estrogen receptor in a variety of normal and pathological tissues. In normal tissue, anti-ER, 1D5 labels estrogen containing cells. Pathological reactivity includes detection of estrogen receptor in breast cancer.

Anti-ER, 1D5 is comparable in use and technology to Abbott ER-ICA Monoclonal, clone H222 which labels cells in tissues and is currently in commercial distribution. Similarities of the anti-ER, 1D5 to the Abbott ER-ICA include that both products are monoclonal antibodies directed against the human Estrogen Receptor (ER). The differences between the two products include that the DAKO anti-ER, 1D5 is directed to the N-terminal end of the ER, while the H222 clone from the Abbott ER-ICA is directed against the functional section of the ER, coded for in exon 5 of the ER DNA. Clone H222 is of rat origin, while anti-ER, 1D5 is of mouse origin. Functionally, anti-ER, 1D5 reacts with an epitope exposed in formalin-fixed, paraffin-embedded tissues by heat induced epitope retrieval. The H222 clone binds to ER found in frozen tissues. When the H222 clone has been tested on formalin-fixed, paraffin-embedded tissues, the specificity was decreased from that seen with frozen tissues.

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The DAKO anti-estrogen receptor, clone 1D5 is substantially equivalent to the Abbott ER-ICA Monoclonal, clone H222 in that both products specifically bind to estrogen receptor proteins located in the nuclei of cells, both products require similar detection chemistry principles for visualization of the product, and both aid in the prognosis of breast carcinoma. Direct comparison is presented in Table 2.

TABLE 2.

| | | |
|---|---|---|
| **DEVICE** | DAKO® Monoclonal Mouse Anti-Human Estrogen Receptor, clone 1D5 (Product Code Nos. M7047 and N1575) | Abbott ER-ICA Monoclonal, clone H222 |
| **ANTIBODY TYPE** | Monoclonal, mouse origin | Monoclonal, rat origin |
| **ISOTYPE** | $IgG_1$, kappa | |
| **CLONE** | 1D5 | H222 |
| **PRESENTATION** | tissue culture supernatant | |
| **REACTIVITY** | estrogen receptor | estrogen receptor |
| **POSITIVE CELL TYPE** | cells containing estrogen | cells containing estrogen |
| **STAINING PATTERN** | nuclear | nuclear |
| **INTENDED USE** | semi-quantitative detection of estrogen receptor | semi-quantitative detection of estrogen receptor |
| **CLINICAL UTILITY** | aid in prognosis and management of breast cancer | aid in prognosis and management of breast cancer |
| **TECHNOLOGY** | qualitative and semi-quantitative immunohistochemistry | qualitative and semi-quantitative immunohistochemistry |
| **INTERPRETATION** | light microscopy | light microscopy |
| **SPECIMEN TYPES** | paraffin embedded tissue and cryostat | cryostat |
| **STORAGE** | 2-8°C | 2-8°C |



AP 11-17-99

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

MAR - 3 2000

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

Re: K993957
Trade Name: DAKO® Monoclonal Mouse Anti-Human Estrogen Receptor, Clone 1D5, Antibody for Immunoenzymatic Staining (Product Code No. M7047) and DAKO® Monoclonal Mouse Anti-Human Estrogen Receptor, Clone 1D5, Ready-to-Use Antibody and Negative Control Reagent for Immunoenzymatic Staining (Product Code No. N1575)
Regulatory Class: II
Product Code: MYA
Dated: February 4, 2000
Received: February 17, 2000

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 legally marketed predicate 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 requirements, 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.

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" (21CFR 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 (301) 443-6597 or at its internet address "http://www.fda.gov/cdrh/dsma/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):** K993957

**Device Name:** Monoclonal Mouse Anti-Human Estrogen Receptor, Clone 1D5 Antibody for Immunoenzymatic Staining (DAKO Code No. M7047)

Monoclonal Mouse Anti-Human Estrogen Receptor, Clone 1D5 Ready-to-Use Antibody and Negative Control for Immunoenzymatic Staining (DAKO Code No. N1575)

## Indications For Use:

Monoclonal Mouse Anti-Human Estrogen Receptor, Clone 1D5 may be used in the semi-quantitative detection of human estrogen receptor in tissue sections of human breast cancer by immunohistochemistry. The information gained by this assay can aid in assessing the likelihood of response to therapy as well as in the prognosis and management of breast cancer patients.

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)

**Concurrence of CDRH, Office of Device Evaluation (ODE)**

Peter C. Mahon

**(Division Sign-Off)**
**Division of Clinical Laboratory Devices**
**510(k) Number** K993957

**Prescription Use** ✓ OR **Over-The-Counter Use** ___
(Per 21 CFR 801.109) (Per 21 CFR 801.110

**IVD Use** ✓
(Per 21 CFR 801.119

(Optional Format 1-2-96)