CONFIRM anti-Estrogen Receptor (ER) (SP1) Rabbit Monoclonal Primary Antibody

REF 790-4324 Σ 50

05278406001

REF 790-4325 Σ 250

05278414001

IVD

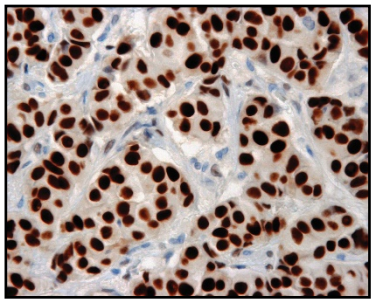

Figure 1. CONFIRM anti ER (SP1) antibody staining of breast lobular carcinoma.

INTENDED USE

CONFIRM anti-Estrogen Receptor (ER) (SP1) Rabbit Monoclonal Primary Antibody (CONFIRM anti-ER (SP1) antibody) is intended for laboratory use in the qualitative detection of estrogen receptor (ER) antigen in sections of formalin-fixed, paraffin-embedded breast tissue on a VENTANA automated slide stainer with VENTANA detection kits and ancillary reagents. CONFIRM anti-ER (SP1) antibody is directed against an epitope present on human ER alpha protein located in the nucleus of ER positive normal and neoplastic cells. CONFIRM anti-ER (SP1) antibody is indicated as an aid in the management, prognosis, and prediction of hormone therapy for breast carcinoma.

This product should be interpreted by a qualified pathologist in conjunction with histological examination, relevant clinical information, and proper controls.

Prescription use only.

This antibody is intended for in vitro diagnostic (IVD) use.

SUMMARY AND EXPLANATION

CONFIRM anti-ER (SP1) antibody is a rabbit monoclonal antibody that recognizes human estrogen receptor (ER) alpha. ER is a nuclear hormone receptor encoded by two distinct genes, ESR1 and ESR2, that transcribe alpha and beta isoforms respectively.[1,2] ER alpha is the primary isoform expressed in luminal epithelial cells in breast tissue.[1,2] ER activity drives normal mammary gland development and is required for differentiation and proliferation in the adult breast epithelium.[3,4] In neoplastic cells upregulated ER activity, induced by overexpression of the receptor, initiates a cascade of cellular events that result in hyper proliferation and tumor formation.[5]

Breast cancer is the leading cause of cancer related death in women.[6] The diagnosis and treatment of the disease relies on early detection coupled with an appropriate treatment strategy based on prognostic and predictive factors.[7,8] ER was identified as a prognostic indicator in breast cancer in 1973 and its value in predicting response to endocrine therapy was evaluated in a large cohort in 1986.[9,10] ER has since become one of the paradigm tumor markers for the management of patients with breast cancer. A high ER concentration on the mammary tumor correlates with greater response to endocrine therapy.[7,8] The knowledge of ER status plays an important role in the selection of treatment for the patient but is not the sole basis for treatment selection.[7,8] It has been shown in a number of studies that the presence of ER confers a favorable long term prognosis.[10,11]

Clinical guidelines and best practice recommendations stipulate that ER status should be evaluated in every case of primary invasive breast cancer to identify patients most likely to respond to endocrine forms of therapy.[7,8] Selective estrogen receptor modulators block estrogen mediated cancer growth by mitigating ER hyperactivity and are used as endocrine (hormone) therapy for patients overexpressing the receptor.[8,12] Currently, the treatment of choice for ER positive carcinomas is tamoxifen.[7,8]

Guidelines and best practice recommendations emphasize that immunohistochemistry (IHC) is the preferred method to detect ER in breast cancer.[13] Studies of large cohorts of invasive breast cancer cases conclude that anti-ER clone SP1 is more sensitive for ER detection than mouse monoclonal clones 1D5 and 6F11.[14,15] The IHC-based detection of ER with CONFIRM anti-ER (SP1) antibody may be used as an aid in the management, prognosis and prediction of hormone therapy for breast carcinoma.

PRINCIPLE OF THE PROCEDURE

CONFIRM anti-ER (SP1) antibody binds to ER in formalin-fixed, paraffin-embedded (FFPE) tissue sections. The specific antibody can be localized by either a biotin conjugated secondary antibody formulation that recognizes rabbit immunoglobulins, followed by the addition of a streptavidin horseradish peroxidase (HRP) conjugate (*i*VIEW DAB Detection Kit) or a secondary antibody-HRP conjugate (*ultra*View Universal DAB Detection Kit). The specific antibody-enzyme complex is then visualized with a precipitating enzyme reaction product. Clinical cases should be evaluated within the context of the performance of appropriate controls. Ventana recommends the inclusion of a positive tissue control fixed and processed in the same manner as the patient specimen (for example, a weakly positive breast carcinoma or uterus). In addition to staining with CONFIRM anti-ER (SP1) antibody, a second slide should be stained with CONFIRM Negative Control Rabbit Ig. For the test to be considered valid, the positive control tissue should exhibit nuclear staining of the tumor cells or uterine glands and stroma. These components should be negative when stained with CONFIRM Negative Control Rabbit Ig. In addition, it is recommended that a negative tissue control slide (for example, an ER negative breast carcinoma) be included for every batch of samples processed and run on a BenchMark IHC/ISH instrument. This negative tissue control should be stained with CONFIRM anti-ER (SP1) antibody to ensure that the antigen enhancement and other pretreatment procedures did not create false positive staining.

MATERIAL PROVIDED

CONFIRM anti-ER (SP1) antibody (Cat. No. 790-4324) contains sufficient reagent for 50 tests.

One 5 mL dispenser of CONFIRM anti-ER (SP1) antibody contains approximately 5 µg of a rabbit monoclonal antibody directed against human ER antigen.

CONFIRM anti-ER (SP1) antibody (Cat. No. 790-4325) contains sufficient reagent for 250 tests.

One 25 mL dispenser CONFIRM anti-ER (SP1) antibody contains approximately 25 µg of a rabbit monoclonal antibody directed against human ER antigen.

The antibody is diluted in Tris-HCl with carrier protein, and 0.10% ProClin 300, a preservative. There is trace (~0.2%) fetal calf serum of United States origin from the stock solution.

Specific antibody concentration is approximately 1 µg/mL. There is no known non-specific antibody reactivity in this product.

CONFIRM anti-ER (SP1) antibody is a rabbit monoclonal antibody produced as a cell culture supernatant.

Refer to the appropriate VENTANA detection kit method sheet for detailed descriptions of: Principle of the Procedure, Material and Methods, Specimen Collection and Preparation for Analysis, Quality Control Procedures, Troubleshooting, Interpretation of Results, and Limitations.

MATERIALS REQUIRED BUT NOT PROVIDED

Staining reagents, such as VENTANA detection kits and ancillary components, including negative and positive tissue control slides, are not provided.

Not all products listed in the method sheet may be available in all geographies. Consult your local support representative.

The following reagents and materials may be required for staining but are not provided:

1. Recommended control tissue
2. Microscope slides, positively charged
3. CONFIRM Negative Control Rabbit Ig (Cat. No. 760-1029 / 05266238001)
4. *ultra*View Universal DAB Detection Kit (Cat. No. 760-500 / 05269806001)
5. *i*VIEW DAB Detection Kit (Cat. No. 760-091 / 05266157001)
6. A/B Block (Endogenous Biotin Blocking Kit) (Cat. No. 760-050 / 05266092001)
7. EZ Prep Concentrate (10X) (Cat. No. 950-102 / 05279771001)
8. Reaction Buffer Concentrate (10X) (Cat. No. 950-300 / 05353955001)
9. LCS (Predilute) (Cat. No. 650-010 / 05264839001)
10. ULTRA LCS (Predilute) (Cat. No. 650-210 / 05424534001)

11. Cell Conditioning Solution (CC1) (Cat. No. 950-124 / 05279801001)
12. ULTRA Cell Conditioning Solution (ULTRA CC1) (Cat. No. 950-224 / 05424569001)
13. Hematoxylin II (Cat. No. 790-2208 / 05277965001)
14. Bluing Reagent (Cat. No. 760-2037 / 05266769001)
15. BenchMark IHC/ISH instrument
16. General purpose laboratory equipment

STORAGE AND STABILITY

Upon receipt and when not in use, store at 2-8°C. Do not freeze.

To ensure proper reagent delivery and the stability of the antibody, replace the dispenser cap after every use and immediately place the dispenser in the refrigerator in an upright position.

Every antibody dispenser is expiration dated. When properly stored, the reagent is stable to the date indicated on the label. Do not use reagent beyond the expiration date.

SPECIMEN PREPARATION

Routinely processed FFPE tissues are suitable for use with this primary antibody when used with VENTANA detection kits and BenchMark IHC/ISH instruments. The following steps are recommended for processing specimens:[16]

1. Place specimen in 10% neutral buffered formalin. The amount used is 15 to 20 times the volume of tissue. No fixative will penetrate more than 2 to 3 mm of solid tissue or 5 mm of porous tissue in a 24-hour period. A 3 mm or smaller section of tissue should be fixed no less than 4 hours and no more than 8 hours. Fixation can be performed at room temperature (15-25°C).
2. After fixation, the specimen is placed in a tissue processing instrument for overnight preparation. Briefly, this processing consists of dehydration of the specimen with alcohols followed by clearing reagents to remove alcohols and finally infiltration with paraffin.
3. Samples are embedded with paraffin in tissue cassettes and approximately 4 µm thick sections are cut, centered and picked up on glass slides. The slides should be Superfrost Plus or equivalent. Tissue should be air dried by placing the slides at ambient temperature overnight or placed in a 60°C oven for 30 minutes.

Slides should be stained immediately, as antigenicity of cut tissue sections may diminish over time.

It is recommended that positive and negative tissue controls be run simultaneously with unknown specimens.

WARNINGS AND PRECAUTIONS

1. For in vitro diagnostic (IVD) use.
2. For professional use only.
3. **CAUTION**: In the United States, Federal law restricts this device to sale by or on the order of a physician. (Rx Only)
4. Do not use beyond the specified number of tests.
5. ProClin 300 solution is used as a preservative in this reagent. It is classified as an irritant and may cause sensitization through skin contact. Take reasonable precautions when handling. Avoid contact of reagents with eyes, skin, and mucous membranes. Use protective clothing and gloves.
6. Positively charged slides may be susceptible to environmental stresses resulting in inappropriate staining. Ask your Roche representative for more information on how to use these types of slides.
7. This product contains 1% or less bovine serum, which is used in the manufacture of the antibody.
8. Materials of human or animal origin should be handled as biohazardous materials and disposed of with proper precautions. In the event of exposure, the health directives of the responsible authorities should be followed.[17,18]
9. Avoid contact of reagents with eyes and mucous membranes. If reagents come in contact with sensitive areas, wash with copious amounts of water.
10. Avoid microbial contamination of reagents as it may cause incorrect results.
11. For further information on the use of this device, refer to the BenchMark IHC/ISH instrument User Guide, and instructions for use of all necessary components located at dialog.roche.com.
12. Consult local and/or state authorities with regard to recommended method of disposal.
13. Product safety labeling primarily follows EU GHS guidance. Safety data sheet available for professional user on request.
14. To report suspected serious incidents related to this device, contact the local Roche representative and the competent authority of the Member State or Country in which the user is established.

This product contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

Table 1. Hazard information.

Hazard	Code	Statement
Warning 	H317	May cause an allergic skin reaction.
	H412	Harmful to aquatic life with long lasting effects.
	P261	Avoid breathing mist or vapours.
	P273	Avoid release to the environment.
	P280	Wear protective gloves.
	P333 + P313	If skin irritation or rash occurs: Get medical advice/ attention.
	P362 + P364	Take off contaminated clothing and wash it before reuse.
	P501	Dispose of contents/ container to an approved waste disposal plant.

This product contains CAS # 55965-84-9, reaction mass of 5-chloro-2-methyl-2H-isothiazol-3-one and 2-methyl-2H-isothiazol-3-one (3:1).

STAINING PROCEDURE

VENTANA primary antibodies have been developed for use on BenchMark IHC/ISH instruments in combination with VENTANA detection kits and accessories. Refer to Table 2 and Table 3 for recommended staining protocols.

This antibody has been optimized for specific incubation times but the user must validate results obtained with this reagent.

The parameters for the automated procedures can be displayed, printed and edited according to the procedure in the instrument User Guide. Refer to the appropriate VENTANA detection kit method sheet for more details regarding IHC staining procedures.

For more details on the proper use of this device, refer to the inline dispenser method sheet associated with P/N 790-4324, or P/N 790-4325.

Verification and validation of the recommended staining procedure for each detection kit is demonstrated through design control testing and results of clinical studies.

Any modification to the recommended staining procedure nullifies the Performance Characteristics provided in this method sheet. The user must accept responsibility for any modification to the recommended staining procedure.

Table 2. Recommended staining protocols for CONFIRM anti-ER (SP1) antibody using *ultra*View Universal DAB Detection Kit on BenchMark IHC/ISH instruments.

Procedure Type	Method	
	XT	ULTRA or ULTRA PLUS
Deparaffinization	Selected	Selected
Cell Conditioning (Antigen Unmasking)	CC1, Standard	ULTRA CC1, Standard
Antibody (Primary)	16 minutes, 37°C	16 minutes, 36°C
Counterstain	Hematoxylin II, 4 minutes	Hematoxylin II, 4 minutes
Post Counterstain	Bluing, 4 minutes	Bluing, 4 minutes

Table 3. Recommended staining protocols for CONFIRM anti-ER (SP1) antibody using *i*VIEW DAB Detection Kit on BenchMark IHC/ISH instruments

Procedure Type	Method	
	XT	ULTRA
Deparaffinization	Selected	Selected
Cell Conditioning (Antigen Unmasking)	CC1, Standard	ULTRA CC1, Standard
Antibody (Primary)	16 minutes, 37°C	16 minutes, 36°C
A/B Block (Biotin Blocking)	Required	Required
Counterstain	Hematoxylin II, 4 minutes	Hematoxylin II, 4 minutes
Post Counterstain	Bluing, 4 minutes	Bluing, 4 minutes

Due to variation in tissue fixation and processing, as well as general lab instrument and environmental conditions, it may be necessary to increase or decrease the primary antibody incubation, cell conditioning or protease pretreatment based on individual specimens, detection used, and reader preference. For further information on fixation variables, refer to "Immunohistochemistry Principles and Advances."[19]

POSITIVE TISSUE CONTROL

A positive tissue control must be included with each staining run. The College of American Pathologists recommends that a positive tissue control should be on the patient slide.[13] An example of tissue to use as a positive control with CONFIRM anti-ER (SP1) antibody is a weakly positive breast carcinoma. The positive staining cells or tissue components (nuclear staining of tumor cells) are used to confirm that CONFIRM anti-ER (SP1) antibody was applied and the instrument functioned properly. This tissue may contain both positive and negative staining cells or tissue components and serve as both the positive and negative control tissue. Control tissues should be fresh autopsy, biopsy or surgical specimens prepared or fixed as soon as possible in a manner identical to the test sections. Such tissues may monitor all steps of the procedure, from tissue preparation through staining. Use of a tissue section fixed or processed differently from the test specimen will provide control for all reagents and method steps except fixation and tissue processing.

A tissue with weak positive staining is more suitable than strong positive staining for optimal quality control and for detecting minor levels of reagent degradation. Ideally, a breast carcinoma tissue, which is known to have weak but positive staining should be chosen to ensure that the system is sensitive to small amounts of reagent degradation or problems with the IHC methodology.

Alternatively, normal human proliferative endometrium may be used for a positive control. The positive staining components are nuclear staining of the glandular epithelia, and stromal and smooth muscle cells. Endometrial tissue, however, may not stain weakly enough to detect small amounts of reagent degradation or problems with the IHC methodology.

Optimal laboratory practice is to include a positive control section on the same slide as the test tissue. This helps identify any failures applying reagents to the slide. Tissue with weak positive staining is best suited for quality control.

Known positive tissue controls should be utilized only for monitoring the correct performance of processed tissues and test reagents, and not as an aid in determining a specific diagnosis of patient samples. If the positive tissue controls fail to demonstrate positive staining, results with the test specimens should be considered invalid.

NEGATIVE TISSUE CONTROL

Use a tissue control known to be fixed, processed and embedded in a manner identical to the patient sample(s) with each staining run to verify the specificity of CONFIRM anti-ER (SP1) antibody for demonstration of ER, and to provide an indication of specific background staining (false positive staining). Also the variety of different cell types in most tissue sections can be used as internal negative control to verify CONFIRM anti-ER (SP1) antibody performance specifications. For example, the same tissue (endometrium) used for the positive tissue control may be used as the negative tissue control. The components that do not stain (cytoplasm, cell membrane) should show absence of specific staining in cells not expected to stain, and provide an indication of specific background staining. The negative tissue control also should be used as an aid in interpretation of results. The variety of different cell types present in most tissue sections frequently offers negative control sites, but this should be verified by the user. If specific staining occurs in the negative tissue control sites, results with the patient specimens should be considered invalid.

NEGATIVE REAGENT CONTROL

A negative reagent control must be run for every specimen to aid in the interpretation of results. A negative reagent control is used in place of the primary antibody to evaluate nonspecific staining and allow better interpretation of specific staining at the antigen site. This provides an indication of nonspecific background staining for each slide. In place of the primary antibody, stain the slide with CONFIRM Negative Control Rabbit Ig, a purified non-immune rabbit IgG not reacting with human specimens. If an alternative negative reagent control is used, dilute to the same dilution as the primary antibody antiserum with Antibody Diluent. Approximately 0.2% fetal calf serum is retained in the CONFIRM anti-ER (SP1) antibody. Addition of 0.2% fetal calf serum in Antibody Diluent is also suitable for use as a nonspecific negative reagent control. The incubation period for the negative reagent control should equal the primary antibody.

When panels of several antibodies are used on serial sections, a negative reagent control on one slide may serve as a negative or nonspecific binding background control for other antibodies.

ASSAY VERIFICATION

Prior to initial use of this antibody in a diagnostic procedure, or if there is a change of lot number, the specificity of the antibody should be verified by staining a number of positive and negative tissues with known performance characteristics. Refer to the quality control procedures previously outlined in this section of the product insert and to the quality control recommendations of the College of American Pathologists Laboratory Accreditation Program, Anatomic Pathology Checklist, or the CLSI Approved Guideline or both documents.[20,21] These quality control procedures should be repeated for each new antibody lot or whenever there is a change of lot number of one of the reagents in a matched set or a change in assay parameters. Quality control cannot be meaningfully performed on an individual reagent in isolation since the matched reagents, along with a defined assay protocol, must be tested in unison before using a kit for diagnostic purposes. Tissues listed in the Summary of Expected Results are suitable for assay verification.

All quality control requirements should be performed in conformance with local, state and federal regulations or accreditation requirements.

STAINING INTERPRETATION / EXPECTED RESULTS

The VENTANA automated immunostaining procedure causes a colored reaction product to precipitate at the antigen sites localized by CONFIRM anti-ER (SP1) antibody. A qualified pathologist experienced in immunohistochemistry procedures must evaluate positive and negative controls and qualify the stained product before interpreting results. Estrogen receptor status is determined by the percentage of stained tumor cells. A case is considered ER positive if there is staining of the nucleus in equal to or greater than 1% of tumor cells.[13] Specific staining of stroma and lymphocytes may be observed. It is imperative that only nuclear staining in tumor cells be considered when scoring these slides.

Positive Tissue Control

The positive tissue control stained with CONFIRM anti-ER (SP1) antibody should be examined first to ascertain that all reagents are functioning properly. The presence of a brown (3,3' diaminobenzidine tetrachloride, DAB) reaction product within the target cells' nuclei is indicative of positive reactivity. An example of a tissue that may be used as a positive control is a known weakly positive breast carcinoma, e.g., ≥ 1% in which nuclei of the tumor cells should be positive. Normal human endometrium may also be used. In normal endometrium, ER staining is seen in nuclei of the endometrial glands and stroma. If the positive tissue controls fail to demonstrate appropriate positive staining, any results with the test specimens should be considered invalid.

Negative Tissue Control

The negative tissue control should be examined after the positive tissue control to verify the specific labeling of the target antigen by the primary antibody. The absence of specific staining in the negative tissue control confirms the lack of antibody cross reactivity to cells or cellular components. The breast carcinoma used as a positive control may also be used as a negative control tissue. Certain stromal elements known to be ER negative such as

endothelial cells should show no nuclear staining. If specific staining occurs in the negative tissue control, results with the patient specimen should be considered invalid.

Nonspecific staining, if present, will have a diffuse appearance. Sporadic light staining of connective tissue may also be observed in tissue sections that are excessively formalin fixed. Intact cells should be used for interpretation of staining results, as necrotic or degenerated cells will often stain nonspecifically.[22]

Patient Tissue

Patient specimens stained with CONFIRM anti-ER (SP1) antibody should be examined last. Positive staining intensity should be assessed within the context of any nonspecific background staining of the negative reagent control. ER may be detected among other neoplasms, such as cancers of the ovary and endometrium.[13] The morphology of each tissue sample should also be examined utilizing a hematoxylin and eosin stained section when interpreting any immunohistochemical result. The patient's morphologic findings and pertinent clinical data must be interpreted by a qualified pathologist. Refer to Summary and Explanation, Limitations, and Summary of Expected Results for specific information regarding immunoreactivity.

LIMITATIONS

General Limitations

1. IHC is a multiple step diagnostic process that requires specialized training in the selection of the appropriate reagents and tissues, fixation, processing, preparation of the immunohistochemistry slide, and interpretation of the staining results.
2. Tissue staining is dependent on the handling and processing of the tissue prior to staining. Improper fixation, freezing, thawing, washing, drying, heating, sectioning, or contamination with other tissues or fluids may produce artifacts, antibody trapping, or false negative results. Inconsistent results may be a consequence of variations in fixation and embedding methods, or from inherent irregularities within the tissue.
3. Excessive or incomplete counterstaining may compromise proper interpretation of results.
4. The clinical interpretation of any positive staining, or its absence, must be evaluated within the context of clinical history, morphology and other histopathological criteria. The clinical interpretation of any staining, or its absence, must be complemented by morphological studies and proper controls as well as other diagnostic tests. This antibody is intended to be used in a panel of antibodies. It is the responsibility of a qualified pathologist to be familiar with the antibodies, reagents and methods used to produce the stained preparation. Staining must be performed in a certified, licensed laboratory under the supervision of a pathologist who is responsible for reviewing the stained slides and assuring the adequacy of positive and negative controls.
5. Ventana provides antibodies and reagents at optimal dilution for use when the provided instructions are followed. Any deviation from recommended test procedures may invalidate expected results. Appropriate controls must be employed and documented. Users who deviate from recommended test procedures must accept responsibility for interpretation of patient results.
6. This product is not intended for use in flow cytometry, performance characteristics have not been determined.
7. Reagents may demonstrate unexpected reactions in previously untested tissues. The possibility of unexpected reactions even in tested tissue groups cannot be completely eliminated because of biological variability of antigen expression in neoplasms, or other pathological tissues.[22] Contact your local support representative with documented unexpected reactions.
8. Tissues from persons infected with hepatitis B virus and containing hepatitis B surface antigen (HBsAg) may exhibit nonspecific staining with horseradish peroxidase.[23]
9. When used in blocking steps, normal sera from the same animal source as the secondary antisera may cause false negative or false positive results due to autoantibodies or natural antibodies.
10. False positive results may be seen because of non-immunological binding of proteins or substrate reaction products. They may also be caused by pseudoperoxidase activity (erythrocytes), endogenous peroxidase activity (cytochrome C), or endogenous biotin (example: liver, brain, breast, kidney) depending on the type of immunostain used.[24]
11. As with any IHC test, a negative result means that the antigen was not detected, not that the antigen was absent in the cells or tissue assayed.

SPECIFIC LIMITATIONS

1. The antibody, in combination with VENTANA detection kits and accessories, detects antigen that survives routine formalin fixation, tissue processing and sectioning. Users who deviate from recommended test procedures are responsible for interpretation and validation of patient results.
2. A CONFIRM anti-ER (SP1) antibody negative result does not exclude the presence of ER. Negative reactions in breast carcinomas may be due to loss or marked decrease of expression of antigen. Therefore, it is recommended that this antibody be used in a panel of antibodies including progesterone receptor.
3. All assays might not be registered on every instrument. Please contact your local Roche representative for more information.

PERFORMANCE CHARACTERISTICS

ANALYTICAL PERFORMANCE

Staining tests for sensitivity, specificity, and precision were conducted and the results are listed below.

Sensitivity and Specificity

Immunoreactivity of CONFIRM anti-ER (SP1) antibody was determined by staining multiple cases of normal human tissues. The results are listed in Table 4.

Table 4. Sensitivity/Specificity of CONFIRM anti-ER (SP1) antibody was determined by testing FFPE normal tissues.

Tissue	# positive / total cases	Tissue	# positive / total cases
Cerebrum	0/5	Esophagus	0/3
Cerebellum	0/3	Stomach	0/3
Adrenal gland	0/3	Small intestine	0/3
Ovary	1/3	Colon	0/3
Pancreas	0/3	Liver	0/3
Parathyroid gland	0/4	Salivary gland	0/3
Pituitary gland	3/3	Kidney	0/3
Testis	0/3	Prostate	2/3
Thyroid	1/5	Bladder	0/5
Breast [a]	12/12	Endometrium	3/3
Spleen	0/3	Cervix	1/3
Tonsil	1/3	Skeletal muscle	0/3
Thymus	0/3	Skin [b]	0/5
Bone marrow	0/3	Nerve	0/3
Lung	0/3	Mesothelium	0/3
Heart	0/3		

[a] Tissue include fibrofatty tissue.

[b] Tissue include nipple.

Immunoreactivity of CONFIRM anti-ER (SP1) antibody was determined by staining multiple cases of neoplastic human tissues. Cases were considered ER positive if there was staining of the nucleus in at least ≥ 1% of invasive tumor cells.[13] The results are listed in Table 5.

Table 5. Sensitivity/Specificity of CONFIRM anti-ER (SP1) antibody was determined by testing a variety of FFPE neoplastic tissues.

Pathology	# positive / total cases
Glioblastoma (Cerebrum)	0/1
Meningioma (Cerebrum)	0/1
Ependymoma (Cerebrum)	0/1
Oligodendroglioma (Cerebellum)	0/1
Serous adenocarcinoma (Ovary)	0/1
Mucinous adenocarcinoma (Ovary)	0/1
Neuroendocrine neoplasm (Pancreas)	0/1
Adenocarcinoma (Pancreas)	0/1
Seminoma (Testis)	0/1
Embryonal carcinoma (Testis)	0/1
Medullary carcinoma (Thyroid)	0/1
Papillary carcinoma (Thyroid)	0/1
Ductal carcinoma in situ (Breast)	1/3
Invasive ductal carcinoma (Breast)	9/20
Invasive lobular carcinoma (Breast)	2/3
Medullary carcinoma (Breast)	0/1
Papillary carcinoma (Breast)	1/1
Breast carcinoma (Metastatic)	0/5
B-Cell Lymphoma; NOS (Spleen)	0/1
Small cell carcinoma (Lung)	0/1
Squamous cell carcinoma (Lung)	0/1
Adenocarcinoma (Lung)	0/1
Squamous cell carcinoma (Esophagus)	0/1
Adenocarcinoma (Esophagus)	0/1
Mucinous adenocarcinoma (Stomach)	0/1
Adenocarcinoma (Intestine)	0/1
Malignant mixed mesenchymal neoplasm (Intestine)	0/1
Adenocarcinoma (Colon)	0/1
Malignant mixed mesenchymal neoplasm (Colon)	0/1
Adenocarcinoma (Rectum)	0/1
Malignant mixed mesenchymal neoplasm (Rectum)	0/1
Melanoma (Rectum)	0/1
Hepatocellular carcinoma (Liver)	0/1
Hepatoblastoma (Liver)	0/1
Clear cell carcinoma (Kidney)	0/1
Adenocarcinoma (Prostate)	1/1
Urothelial carcinoma (Prostatic urethra)	1/1
Leiomyoma (Uterus)	1/1
Adenocarcinoma (Uterus)	2/2
Clear cell carcinoma (Uterus)	0/1
Squamous cell carcinoma (Cervix)	0/1
Embryonal rhabdomyosarcoma (Striated muscle)	0/1
Basal cell carcinoma (Skin)	0/1
Squamous cell carcinoma (Striated muscle)	0/1
Neurofibroma (Mediastinum)	0/1
Neuroblastoma (Retroperitoneum)	0/1
Spindle cell rhabdomyosarcoma (Retroperitoneum)	0/1
Mesothelioma (Peritoneum)	0/1
Hodgkin lymphoma (Lymph node)	0/1
Lymphoma, NOS (Lymph node)	0/2
B-cell lymphoma, NOS (Lymph node)	0/1
Urothelial carcinoma (Bladder)	0/1
Osteosarcoma (Bone)	0/1
Leiomyosarcoma (Smooth muscle)	0/1

Sensitivity is dependent upon the preservation of the antigen. Any improper tissue handling during fixation, sectioning, embedding or storage which alters antigenicity weakens ER detection by CONFIRM anti-ER (SP1) antibody and may generate false negative results.

BenchMark XT and BenchMark ULTRA Instrument Precision

Six individual tissues cases were stained as part of the precision testing. Of the six tissues, two had ER high expression, two had ER low expression, and two were ER negative based on a cutoff of < 1% tumor cells staining for negative, 1-10% for low and > 10% for high expression.

For within-run repeatability testing, 9 slides from each case were stained with CONFIRM anti-ER (SP1) antibody, and one slide from each case was stained with CONFIRM Negative Control Rabbit Ig antibody on a BenchMark XT instrument. The same testing configuration was also performed on a BenchMark ULTRA instrument. Within-run repeatability of CONFIRM anti-ER (SP1) antibody on both BenchMark XT and BenchMark ULTRA instruments was 100% concordant on all positive tissues across six cases. CONFIRM Negative Control Rabbit Ig stained slides were acceptable for signal and background.

For between-day intermediate precision testing, four slides from each case were stained with the CONFIRM anti-ER (SP1) antibody, and one slide from each case was stained with CONFIRM Negative Control Rabbit Ig antibody in five separate non-consecutive runs conducted over a 20 day period on the same BenchMark XT instrument. The same testing configuration was also performed on a BenchMark ULTRA instrument. Between-day intermediate precision of CONFIRM anti-ER (SP1) antibody on both BenchMark XT and BenchMark ULTRA instruments was 100% concordant on all positive tissues across six cases. CONFIRM Negative Control Rabbit Ig stained slides were acceptable for signal and background.

For BenchMark XT between-instrument intermediate precision testing, 4 slides from six cases were stained with CONFIRM anti-ER (SP1) antibody across three separate BenchMark XT instruments. A single slide from each case was stained with CONFIRM Negative Control Rabbit Ig antibody. Between instrument intermediate precision of CONFIRM anti-ER (SP1) antibody on three BenchMark XT instruments was 100%

concordant on all six cases. CONFIRM Negative Control Rabbit Ig stained slides were acceptable for signal and background.

For BenchMark ULTRA between-instrument intermediate precision testing, 4 slides from six cases were stained with CONFIRM anti-ER (SP1) antibody across three separate BenchMark ULTRA instruments. A single slide from each case was stained with CONFIRM Negative Control Rabbit Ig antibody. Between-instrument intermediate precision of CONFIRM anti-ER (SP1) antibody on three BenchMark ULTRA instruments was 100% concordant on all six cases. CONFIRM Negative Control Rabbit Ig stained slides were acceptable for signal and background.

BenchMark ULTRA PLUS Instrument Precision

Nine individual tissues cases were stained as part of the precision testing. Of the nine tissues, three had ER high expression, three had ER low expression, and three were ER negative based on a cutoff of < 1% tumor cells staining for negative, 1-10% for low and > 10% for high expression.

For within-run repeatability testing, five slides from each case were stained with CONFIRM anti-ER (SP1) antibody, and one slide from each case was stained with CONFIRM Negative Control Rabbit Ig antibody on a BenchMark ULTRA PLUS instrument. Within-run repeatability of CONFIRM anti-ER (SP1) antibody on the BenchMark ULTRA PLUS instrument was 100% concordant. CONFIRM Negative Control Rabbit Ig stained slides were acceptable for signal and background.

For between-day intermediate precision testing, two slides from each case were stained with the CONFIRM anti-ER (SP1) antibody, and one slide from each case was stained with CONFIRM Negative Control Rabbit Ig antibody in five separate non-consecutive runs conducted over a 20 day period on the same BenchMark ULTRA PLUS instrument. Between-day intermediate precision of CONFIRM anti-ER (SP1) antibody on the BenchMark ULTRA PLUS instrument was 100% concordant. CONFIRM Negative Control Rabbit Ig stained slides were acceptable for signal and background.

For BenchMark ULTRA PLUS between-instrument intermediate precision testing, two slides from each case were stained with CONFIRM anti-ER (SP1) antibody across three separate BenchMark ULTRA PLUS instruments. A single slide from each case was stained with CONFIRM Negative Control Rabbit Ig antibody. Between-instrument intermediate precision of CONFIRM anti-ER (SP1) antibody on three BenchMark ULTRA PLUS instruments was 100%.

Inter-Laboratory Reproducibility

A Inter-Laboratory Reproducibility study for CONFIRM anti-ER (SP1) antibody was conducted using 14 breast cancer slides (8 positive, 2 low positive, 4 negative) run across 3 BenchMark XT and 3 BenchMark ULTRA instruments, using *i*VIEW DAB detection and *ultra*View DAB detection, on each of 5 non-consecutive days over a minimum 20 day period at 3 external laboratories. The specimens were randomized and evaluated by a total of 6 pathologists (2 pathologists per site) for percentage of stained tumor cells. A case was considered ER positive if there was staining of the nucleus in at least 1% of invasive tumor cells.[13]

For Site-to-Site precision, the average positive agreement (APA) and average negative agreement (ANA) rates for CONFIRM anti-ER (SP1) antibody clinical assessment were 94.3% and 87.9%, respectively, on the BenchMark ULTRA instrument with *i*VIEW detection; 94.2% and 85.8%, respectively, on the BenchMark ULTRA instrument with *ultra*View detection; 95.6% and 90.9%, respectively, on the BenchMark XT instrument with *i*VIEW detection; and 94.2% and 85.3%, respectively, on the BenchMark XT instrument with *ultra*View detection.

For between-day precision, the APA and ANA rates for CONFIRM anti-ER (SP1) antibody clinical assessment were 97.9% and 95.5%, respectively, on the BenchMark ULTRA instrument with *i*VIEW detection; 98.4% and 96.2%, respectively, on the BenchMark ULTRA instrument with *ultra*View detection; 98.0% and 95.9%, respectively, on the BenchMark XT instrument with *i*VIEW detection; and 98.2% and 95.5%, respectively, on the BenchMark XT instrument with *ultra*View detection.

For Reader-to-Reader precision, the APA and ANA for CONFIRM anti-ER (SP1) antibody clinical assessment were 95.7% and 90.9%, respectively, on the BenchMark ULTRA instrument with *i*VIEW detection; 94.1% and 85.7%, respectively, on the BenchMark ULTRA instrument with *ultra*View detection; 94.9% and 89.6%, respectively, on the BenchMark XT instrument with *i*VIEW detection; and 93.4% and 83.6%, respectively, on the BenchMark XT instrument with *ultra*View detection.

For between-platform precision across the BenchMark ULTRA and BenchMark XT instruments, APA and ANA rates were 97.8% and 95.5%, respectively, for *i*VIEW detection, and 98.9% and 97.4%, respectively, for *ultra*View detection.

For within-platform precision, APA and ANA rates were 97.9% and 95.2%, respectively, for the BenchMark ULTRA instrument and 97.8% and 95.0%, respectively, for the BenchMark XT instrument.

Comparison of *i*VIEW DAB Detection Kit and *ultra*View Universal DAB Detection Kit using CONFIRM anti-ER (SP1) antibody

CONFIRM anti-ER (SP1) antibody was used to conduct detection comparison testing across two instruments (BenchMark XT and BenchMark ULTRA instruments), using *i*VIEW DAB Detection Kit and *ultra*View Universal DAB Detection Kit. One hundred and ninety-nine (199) tissue cases were used as part of the testing. Of the evaluable cases as determined by BenchMark ULTRA instrument, 111 were positive and 83 were negative as a function of percentage of tumor cells stained. The stained slides were evaluated by pathologists who determined the percentage of stained tumor cells. A case was considered ER positive if there was staining of the nucleus in at least 1% of tumor cells.

The morphology and background acceptability rates were 100% for both detection kits and instruments. Direct comparisons for positive and negative clinical assessment between detection kits, for each instrument are presented in Table 6 for the BenchMark ULTRA instrument and Table 7 for the BenchMark XT instrument.

Table 6. Assessment for *ultra*View Universal DAB Detection Kit versus *i*VIEW DAB Detection Kit on the BenchMark ULTRA instrument.

*ultra*View Universal DAB Detection Kit	*i*VIEW DAB Detection Kit		
	Positive	**Negative**	**Total**
Positive	108	3	111
Negative	3	80	83
Total	111	83	194
	n/N	**% (95% CI)**	
Positive percent agreement	108/111	97.3 (92.4-99.1)	
Negative percent agreement	80/83	96.4 (89.9-98.8)	
Overall percent agreement	188/194	96.6 (93.4-98.6)	

Table 7. Assessment for *ultra*View Universal DAB Detection Kit versus *i*VIEW DAB Detection Kit on the BenchMark XT instrument.

*ultra*View Universal DAB Detection Kit	*i*VIEW DAB Detection Kit		
	Positive	**Negative**	**Total**
Positive	106	5	111
Negative	2	79	81
Total	108	84	192
	n/N	**% (95% CI)**	
Positive percent agreement	106/108	98.1 (93.5-99.5)	
Negative percent agreement	79/84	94.0 (86.8-97.4)	
Overall percent agreement	185/192	96.4 (92.7-98.2)	

Overall agreements of assessment between detection kits for both platforms were 96.9% (n=194) and 96.4% (n=192) for the BenchMark ULTRA and the BenchMark XT instruments, respectively. The *ultra*View Universal DAB Detection Kit compared to *i*VIEW DAB Detection Kit had staining score agreement rates of 93.3% (n=194) and 93.8% (n=192).

Comparison of BenchMark XT Instrument versus BenchMark ULTRA Instrument

A randomized, multi-site, multi-reader study was conducted to compare the staining performance of the CONFIRM anti-ER (SP1) antibody on the BenchMark ULTRA instrument versus the BenchMark XT instrument. One hundred twenty (120) ER negative and 132 ER positive cases of breast cancer, representing the clinical range of the assay,

were randomly assigned to three study sites such that each site received an equal number of cases and each site received cases representing each clinical assessment category. Each site stained its assigned cases with the CONFIRM anti-ER (SP1) antibody on a BenchMark ULTRA instrument and the CONFIRM anti-ER (SP1) antibody on a BenchMark XT instrument. The stained slides were evaluated by pathologists who determined the percentage of stained tumor cells. A case was considered ER positive if there was staining of the nucleus in at least ≥ 1% of invasive tumor cells.[13]

Table 8. CONFIRM anti-ER (SP1) antibody on the BenchMark ULTRA instrument and CONFIRM anti-ER (SP1) antibody on the BenchMark XT instrument.

BenchMark XT instrument	BenchMark ULTRA instrument		
	Positive	Negative	Total
Positive	99	8	107
Negative	11	91	102
Total	110	99	209
	n/N	% (95% CI)	
Positive percent agreement	99/107	92.5 (85.9-96.2)	
Negative percent agreement	91/102	89.2 (81.7-93.9)	
Overall percent agreement	190/209	90.9 (86.2-94.1)	

The morphology acceptability rates for all slides stained in this study were 100% (95% C.I. 98.5%-100%) for the BenchMark ULTRA instrument and 94.0% (95% C.I. 90.4% - 96.4%) for the BenchMark XT instrument. The background acceptability rates were 94.8% (95% C.I. 91.4% - 97.0%) for the BenchMark ULTRA instrument and 90.9% (95% C.I. 86.7%-93.8%) for the BenchMark XT instrument.

Comparison of BenchMark ULTRA Instrument versus BenchMark ULTRA PLUS Instrument

A study was conducted to compare the staining performance of the CONFIRM anti-ER (SP1) antibody on the BenchMark ULTRA PLUS instrument versus the BenchMark ULTRA instrument. One hundred twenty (120) breast carcinoma tissue cases (54 ER positive, 54 ER negative and 12 ER borderline positive), representing the clinical range of the assay, were stained. The stained slides were evaluated by pathologists who determined the percentage of stained tumor cells. A case was considered ER positive if there was staining of the nucleus in at least ≥ 1% of invasive tumor cells.[13] Agreement rates between cases stained on each instrument are presented in Table 9.

Table 9. CONFIRM anti-ER (SP1) antibody on the BenchMark ULTRA PLUS instrument and CONFIRM anti-ER (SP1) antibody on the BenchMark ULTRA instrument (excluding borderline positive cases).

BenchMark ULTRA PLUS instrument	BenchMark ULTRA instrument		
	Positive	Negative	Total
Positive	53	0	53
Negative	0	53	53
Total	53	53	106
	n/N	% (95% CI)	
Positive percent agreement	53/53	100.0 (93.2-100.0)	
Negative percent agreement	53/53	100.0 (93.2-100.0)	
Overall percent agreement	106/106	100.0 (96.5-100.0)	

The morphology acceptability rate for all slides stained in this study was 99.2% (95% C.I. 95.4%-99.9%) for the BenchMark ULTRA PLUS instrument. The background acceptability rate was 100.0% (95% C.I. 96.8%-100.0%) for the BenchMark ULTRA PLUS instrument.

CLINICAL PERFORMANCE

Comparison to Patient Outcome

A randomized, single-site, multi-reader study was conducted using specimens from 511 invasive breast cancer cases retrieved from a clinical cohort of 820 invasive breast cancer patients. Progression-free survival outcomes were compared for patients with different CONFIRM anti-ER (SP1) antibody status determined on the Benchmark ULTRA instrument. Cases were included in the analyses if the patient had a confirmed diagnosis of invasive breast carcinoma and received treatment with primary surgical intervention with or without post-operative local radiation therapy followed by adjuvant tamoxifen endocrine therapy (20 mg p.o./day) for 5 years. Cases were excluded from analyses if diagnostic biopsy or primary surgical tissue specimens were unavailable, if there had been a prior cancer diagnosis (except non-melanoma skin cancer), or if the patient received prior or adjuvant chemotherapy. A total of 1907 tissue microarray cores with primary tumor were stained on the BenchMark ULTRA instrument. The stained slides were evaluated by three independent pathologists who determined the percentage of stained tumor cells. A case was considered ER positive if there was staining of the nucleus in at least ≥ 1% of invasive tumor cells.[13]

In the study, there were 441 patients with Ventana ER positive (ER+) status and 18 patients with Ventana ER negative (ER–) status. A Kaplan-Meier survival plot by CONFIRM anti-ER (SP1) antibody status among the primary survival analysis population showed strong separation between Ventana ER+ and ER– cases. ER+ patients had longer survival times than ER– patients when tamoxifen treatment was administered; the median survival times for ER+ and ER– patients were 101.6 and 47.2 months, respectively. The log-rank test showed that the difference in survival plots was statistically significant (P < 0.001).

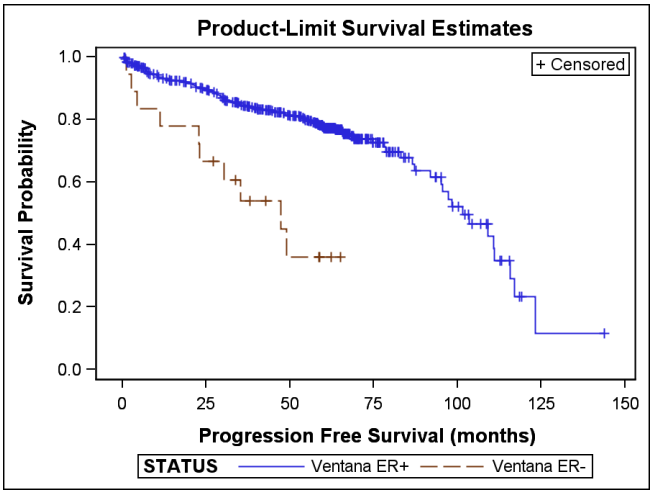

Figure 2. Kaplan-Meier Survival Plot by Ventana ER Status.

TROUBLESHOOTING

1. If the positive control exhibits weaker staining than expected, check the other positive controls run concurrently to determine if it is due to the primary antibody or one of the common secondary reagents.
2. If the positive control is negative, check to ensure that the slide has the proper barcode label. If the slide is labeled properly, check the other positive controls run concurrently to determine if it is due to the primary antibody or one of the common secondary reagents. Tissues may have been improperly collected, fixed or deparaffinized. Follow the proper procedure for collection, storage and fixation.
3. If excessive background staining occurs, high levels of endogenous biotin may be present. A biotin blocking step should be included.
4. If all of the paraffin has not been removed, repeat the deparaffinization procedure.
5. If specific antibody staining is too intense, repeat the run with the primary antibody incubation time shortened by 4 minute intervals to achieve the desired stain intensity.
6. If tissue sections wash off the slide, check slides to ensure that they are positively charged.

7. For corrective action, refer to the Step By Step Procedure section of the instrument User Guide or contact your local support representative.

REFERENCES

1. Paterni I, Granchi C, Katzenellenbogen JA, et al. Estrogen receptors alpha (ERalpha) and beta (ERbeta): subtype-selective ligands and clinical potential. Steroids. 2014;90:13-29.
2. Yasar P, Ayaz G, User SD, et al. Molecular mechanism of estrogen-estrogen receptor signaling. Reprod Med Biol. 2017;16(1):4-20.
3. Tanos T, Rojo L, Echeverria P, et al. ER and PR signaling nodes during mammary gland development. Breast Cancer Res. 2012;14(4):210.
4. Diep CH, Ahrendt H, Lange CA. Progesterone induces progesterone receptor gene (PGR) expression via rapid activation of protein kinase pathways required for cooperative estrogen receptor alpha (ER) and progesterone receptor (PR) genomic action at ER/PR target genes. Steroids. 2016;114:48-58.
5. Carroll JS. Mechanisms of oestrogen receptor (ER) gene regulation in breast cancer. Eur J Endocrinol. 2016;175(1):R41-49.
6. Torre LA, Islami F, Siegel RL, et al. Global Cancer in Women: Burden and Trends. Cancer Epidemiol Biomarkers Prev. 2017;26(4):444-457.
7. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019.
8. Goldhirsch A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol. 2013;24(9):2206-2223.
9. McGuire WL. Estrogen receptors in human breast cancer. J Clin Invest. 1973;52(1):73-77.
10. Vollenweider-Zerargui L, Barrelet L, Wong Y, et al. The predictive value of estrogen and progesterone receptors' concentrations on the clinical behavior of breast cancer in women. Clinical correlation on 547 patients. Cancer. 1986;57(6):1171-1180.
11. Cheang MC, Treaba DO, Speers CH, et al. Immunohistochemical Detection Using the New Rabbit Monoclonal Antibody SP1 of Estrogen Receptor in Breast Cancer Is Superior to Mouse Monoclonal Antibody 1D5 in Predicting Survival. JCO. 2006;24(36):5637-5644.
12. Swaby RF, Sharma CG, Jordan VC. SERMs for the treatment and prevention of breast cancer. Rev Endocr Metab Disord. 2007;8(3):229-239.
13. Hammond ME, Hayes DF, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. Arch Pathol Lab Med. 2010;134(6):907-22.
14. Bae YK, Gong G, Kang J, et al. Hormone Receptor Expression in Invasive Breast Cancer Among Korean Women and Comparison of 3 Antiestrogen Receptor Antibodies - A Multi-institutional Retrospective Study Using Tissue Microarrays. Am J Surg Pathol 2012;36:1817–1825.
15. Bogina G, Zamboni G, Sapino A, et al. Comparison of Anti-Estrogen Receptor Antibodies Sp1, 6f11, and 1d5 in Breast Cancer: Lower 1d5 Sensitivity but Questionable Clinical Implications. Am J Clin Pathol. 2012;138(5):697-702.
16. Carson F, Hladik C. Histotechnology: A Self Instructional Text, 3rd edition. Hong Kong: American Society for Clinical Pathology Press; 2009.
17. Occupational Safety and Health Standards: Occupational exposure to hazardous chemicals in laboratories. (29 CFR Part 1910.1450). Fed. Register.
18. Directive 2000/54/EC of the European Parliament and Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work.
19. Roche PC, Hsi ED. Immunohistochemistry-Principles and Advances. Manual of Clinical Laboratory Immunology, 6th edition. In: NR Rose, ed. ASM Press; 2002.
20. College of American Pathologists Laboratory Accreditation Program, Anatomic Pathology Checklist, 2010.
21. CLSI. Quality Assurance for Immunocytochemistry: Approved Guideline. CLSI document MM4-A- (ISBN 1-56238-396-5). CLSI, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898 USA, 1999.
22. Herman GE, Elfont EA. The taming of immunohistochemistry: the new era of quality control. Biotech Histochem. 1991;66(4):194-199.
23. Omata M, Liew CT, Ashcavai M, Peters RL. Nonimmunologic binding of horseradish peroxidase to hepatitis B surface antigen. A possible source of error in immunohistochemistry. Am J Clin Pathol. 1980;73(5): 626-32.
24. Nadji M, Morales AR. Immunoperoxidase: part 1. The technique and its pitfalls. Lab Med. 1983;14:767.

NOTE: A point (period/stop) is always used in this document as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

The summary of safety and performance can be found here:

https://ec.europa.eu/tools/eudamed

Symbols

Ventana uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see dialog.roche.com for definition of symbols used):

GTIN — Global Trade Item Number

UDI — Unique Device Identifier

Indicates the entity importing the medical device into the European Union

REVISION HISTORY

Rev	Updates
G	Updates to Warnings and Precautions, and Analytical Performance.

INTELLECTUAL PROPERTY

CONTACT INFORMATION

Ventana Medical Systems, Inc.
1910 E. Innovation Park Drive
Tucson, Arizona 85755
USA
+1 520 887 2155
+1 800 227 2155 (USA)

www.roche.com

EC REP

Roche Diagnostics GmbH
Sandhofer Strasse 116
D-68305 Mannheim
Germany
+800 5505 6606

CE 0123