INFORM Cytoplasmic Lambda mRNA Probe

REF 800-2844

05278686001

IVD Σ 50

INTENDED USE

INFORM Cytoplasmic Lambda mRNA Probe is intended for laboratory use in the qualitative in situ hybridization-based detection of Lambda light chain mRNA by light microscopy in sections of formalin-fixed, paraffin-embedded tissue stained on a BenchMark IHC/ISH instrument.

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

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

SUMMARY AND EXPLANATION

INFORM Cytoplasmic Lambda mRNA Probe contains a cocktail of fluorescein-labeled oligonucleotide probes directed against Lambda light chain messenger RNA (mRNA). Lambda light chain proteins are polypeptide chains which, in combination with heavy chains, form immunoglobulin molecules.[1,2,3] There are two classes of light chains found in immunoglobulins: Kappa light chains and Lambda light chains.[2,3] Light chain production by lymphoid cells is genetically restricted such that the immunoglobulin molecules produced by an individual cell will only contain a single light chain class (either Kappa or Lambda) but not both.[2,3] Plasma cell neoplasms often exhibit light chain restriction in which the normal ratio of Kappa to Lambda light chain expressing plasma cells is skewed.[3-6] Detection of clonal mRNA light chain restriction based on the Kappa or Lambda ratio may be used to differentiate monoclonal proliferations, which are often malignant, from polyclonal proliferations that arise during normal reactive immune responses.[3-6]

INFORM Cytoplasmic Lambda mRNA Probe may be used to detect Lambda light chain mRNA expression in the plasma cell population by in situ hybridization (ISH). Determination of the ratio of Kappa to Lambda light chain mRNA expression in this cell population may be used to aid in the differentiation between a reactive process and a plasma cell neoplasm. It may be used along with a panel of immunohistochemistry (IHC) studies.

PRINCIPLE OF THE PROCEDURE

INFORM Cytoplasmic Lambda mRNA Probe is optimally formulated for use with VENTANA ISH iVIEW Blue Detection Kit and accessory reagents on a BenchMark IHC/ISH instrument.

During the Blue ISH staining process, the fluorescein labeled probe is hybridized to specific target RNA sequences in tissues. This step is followed by the addition of a mouse anti-fluorescein antibody which binds to the hapten on the probe. This step is followed by the addition of a biotinylated goat anti-mouse secondary antibody which binds to the anti-fluorescein antibody. This step is followed by the addition of Streptavidin-AP (alkaline phosphatase) enzyme conjugate which binds to the biotin present on the secondary antibody. The fluorescein labeled probe is then visualized with 5-bromo-4-chloro-3-indolyl phosphate (BCIP) and nitro blue tetrazolium (NBT) chromogen, which produces a blue precipitate that is readily detected by light microscopy.

The staining protocol consists of numerous steps in which reagents are incubated for pre-determined times at specific temperatures. At the end of each incubation step, the BenchMark IHC/ISH instrument washes the sections to remove unbound material and applies a liquid coverslip which minimizes the evaporation of the aqueous reagents from the slide. Results are interpreted using a light microscope.

Figure 1 illustrates the Blue ISH reaction.

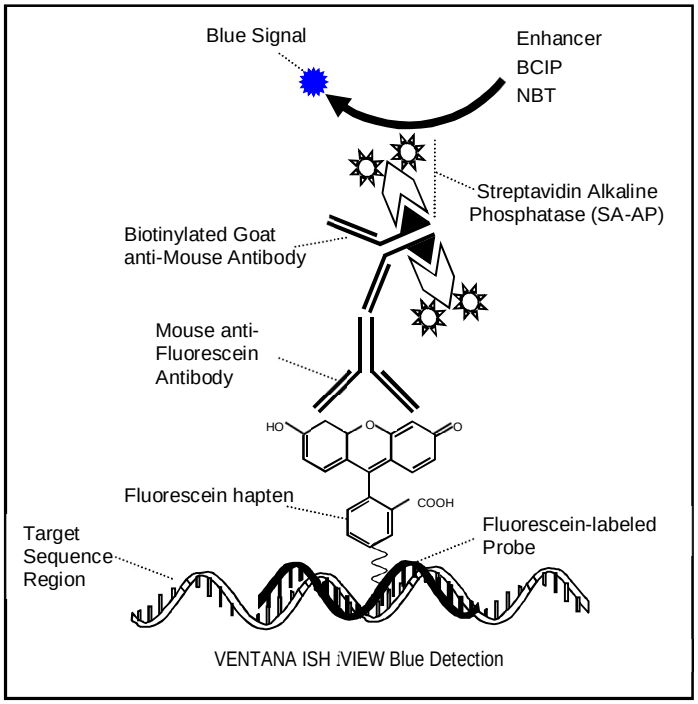

Figure 1. Blue ISH Reaction.

MATERIAL PROVIDED

INFORM Cytoplasmic Lambda mRNA Probe contains sufficient reagent for 50 tests.

One 5 mL dispenser of INFORM Cytoplasmic Lambda mRNA Probe contains approximately 550 ng/mL of the probe labeled with fluorescein, formulated in a formamide-based hybridization buffer.

Refer to the appropriate VENTANA detection kit method sheet for detailed descriptions of: Principles of the Procedure, Materials 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 with the probe kit:

1. RNA Positive Control Probe (Cat. No.800-2846 / 05278708001)
2. Negative Control Probe (Cat. No.800-2847 / 05278716001)
3. Lambda Positive Specimen Slides (Cat. No. 801-2844 / 0527897001)
4. VENTANA ISH iVIEW Blue Detection Kit (Cat. No.800-092 / 05278511001)
5. Reaction Buffer Concentrate (10X) (Cat. No. 950-300 / 05353955001)
6. 10X SSC Solution (Cat. No.950-110 / 05353947001)
7. EZ Prep Concentrate (10X) (Cat. No.950-102 / 05279771001)
8. ULTRA Cell Conditioning Solution (ULTRA CC2) (Cat. No. 950-223 / 05424542001)
9. LCS (Predilute) (Cat. No. 650-010 / 05264839001)
10. ULTRA LCS (Predilute) (Cat. No. 650-210 / 05424534001)
11. ISH Protease 3 (Cat. No.780-4149 / 05273331001)
12. Red Counterstain II (Cat. No. 780-2218 / 05272017001)
13. Microscope slides, positively charged
14. BenchMark IHC/ISH instrument
15. 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 probe, replace the dispenser cap after every use and immediately place the dispenser in the refrigerator in an upright position.

Every probe 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, formalin-fixed, paraffin-embedded (FFPE) tissues are suitable for use with this probe when used with a BenchMark IHC/ISH instrument. The recommended tissue fixative is 10% neutral buffered formalin (NBF).[7] Slides should be stained immediately, as quality of nucleic acid targets in cut tissue sections may diminish over time.

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

Sections thicker than 4 µm may require stronger protease treatment than the recommended condition and may exhibit more nuclear bubbling than thinner sections due to excess paraffin in the tissue. Nuclear bubbling appears as large or small bubbles or vacuoles in the nuclei. Usually this artifact does not interfere with signal enumeration. However, severe cases of nuclear bubbling may distort the nuclei or signals such that enumeration is not possible. These specimens may need to be deparaffinized in xylene and alcohol baths prior to repeat staining on the instrument, or the user may select the extended deparaffinization option in the staining procedure (see Troubleshooting).

WARNINGS AND PRECAUTIONS

1. For in vitro diagnostic (IVD) use.
2. For professional use only.
3. Do not use beyond the specified number of tests.
4. Warning, Product Contains Formamide. Formamide is toxic by inhalation and moderately toxic by ingestion. It is an irritant to skin, eyes, and mucous membranes and is absorbed through the skin. It may cause harm to the unborn child. Take precautions when handling reagents. Use disposable gloves and wear suitable protective clothing when handling suspected carcinogens or toxic materials.
5. Materials of human or animal origin should be handled as potentially biohazardous and disposed of with proper precautions In the event of exposure, the health directives of the responsible authorities should be followed [8,9]
6. Avoid contact of reagents with eyes, skin, and mucous membranes. If reagents come in contact with sensitive areas, wash with copious amounts of water. Avoid inhalation of reagents.
7. Ensure that the waste container is empty prior to starting a run on the instrument. If this precaution is not taken, the waste container may overflow and the user risks a slip and fall.
8. Avoid microbial contamination of reagents as this may produce incorrect results.
9. 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 navifyportal.roche.com.
10. Consult local and/or state authorities to determine the recommended method of disposal.
11. Product safety labeling primarily follows EU GHS guidance. Safety data sheet available for professional user on request.
12. 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
DANGER 	H351	Suspected of causing cancer.
	H360D	May damage the unborn child
	H373	May cause damage to organs through prolonged or repeated exposure.
	P201	Obtain special instructions before use
	P202	Do not handle until all safety precautions have been read and understood.
	P260	Do not breathe mist or vapours.
	P280	Wear protective gloves/ protective clothing/ eye protection/ face protection/ hearing protection.
	P308 + P313	IF exposed or concerned: Get medical advice/ attention.
	P501	Dispose of contents/ container to an approved waste disposal plant.

This product contains CAS# 75-12-7: formamide

STAINING PROCEDURE

VENTANA probes have been developed for use on a BenchMark IHC/ISH instrument in combination with VENTANA detection kits and accessories.

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 ISH staining procedures.

For more details on the proper use of this device, refer to the inline dispenser method sheet associated with P/N 800-2844.

Table 2. Use the following staining procedures to perform INFORM Cytoplasmic Lambda mRNA Probe on BenchMark IHC/ISH instruments.

Instrument Platform	Staining Procedure
BenchMark XT	XT INFORM Probes iVIEW Blue v4
BenchMark ULTRA and BenchMark ULTRA PLUS	U INFORM iVIEW Blue ISH

Table 3. Recommended staining conditions for INFORM Cytoplasmic Lambda mRNA Probe on BenchMark IHC/ISH instruments.

Staining Condition	XT	ULTRA or ULTRA PLUS[a]
Deparaffinization	Selected	Selected
Cell Conditioning Option	CC, Standard	ULTRA CC2, Mild
ISH Protease 3	16 minutes	12 minutes
Probe	INFORM Cytoplasmic Lambda mRNA Probe	INFORM Cytoplasmic Lambda mRNA Probe
Counterstain	Red Counterstain II, 4 minutes	Red Counterstain II, 4 minutes

[a] Concordance was demonstrated between BenchMark ULTRA and BenchMark ULTRA PLUS instruments using representative assays.

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 cell conditioning or protease treatment based on individual specimens, detection used, and reader preference.

QUALITY CONTROL PROCEDURES

Positive Control Specimen

A laboratory-specific positive control specimen may be used with every staining procedure performed. Control specimens should be cytological, biopsy, surgical or fresh autopsy specimens prepared in a manner identical to patient specimens. Such controls are useful to monitor all steps of the procedure, from specimen preparation through staining. If a control specimen is prepared differently from the test specimen then it will provide a control for the reagents, instrument and procedures, not for fixation and specimen processing. Results with the test specimens should be analyzed on the same run.

Negative Control Specimen

A negative control specimen may be run with every staining procedure performed. The purpose is to monitor unintended probe and antibody cross reactivity to cellular components. The same specimen used for the positive control specimen may also be used as the negative control specimen. The variety of different cell types present in most specimens offers internal negative control sites, but this should be verified by the user. The non-staining components should demonstrate absence of specific staining and provide an indication of background staining. If unacceptable staining occurs in the negative control specimen sites, result with the patient specimens should be considered invalid.

Positive Reagent Control

A positive reagent control should be run during assay verification and troubleshooting, since RNA accessibility may vary depending on fixation method and pretreatment of the specimen.

Negative Reagent Control

Negative reagent control should be substituted for the ISH probe with every specimen stained to aid in interpretation of each patient result. This provides an indication of nonspecific background staining for each slide. In place of the ISH probe, stain the slide with Negative Control Probe. The incubation period for controls should correspond to that of the probe.

The negative control is especially important with the finding that the intestinal form of alkaline phosphatase may be found in cells other than the brush border of intestinal epithelial cells. Additionally, enzymes capable of reducing nitro blue tetrazolium may be preserved during fixation.

Unexplained Discrepancies

Unexplained discrepancies in controls should be referred to your local support representative immediately. If quality control results do not meet specifications, patient results are invalid. See the Troubleshooting section of this insert. Identify and correct the problem, then repeat the patient samples.

Assay Verification

Prior to initial use of a reagent in a diagnostic procedure, the performance of the reagent should be verified by testing it on a series of specimens with known ISH performance characteristics (refer to the Quality Control Procedures previously outlined in this section. the Quality Control recommendations of the College of American Pathologists Laboratory Accreditation Program, Anatomic Pathology Checklist,[10] and the NCCLS Approved Guideline[11]). These quality control procedures should be repeated for each new lot of reagents, or whenever there is a change in assay parameters.

STAINING INTERPRETATION / EXPECTED RESULTS

The BenchMark IHC/ISH instrument slide staining procedure causes a blue colored reaction product to precipitate at the target Lambda RNA sites localized by the labeled probe.

A qualified pathologist experienced in the microscopic interpretation of anatomic pathology specimens, and ISH procedures must evaluate controls before interpreting results.

Note: Use of 100X objective is not recommended.

Controls

The stained positive control should be examined first to ascertain that all reagents are functioning properly. The presence of a blue colored reaction product within the target cells is indicative of positive reactivity.

The negative control should be examined after the positive control to verify the specificity of the reaction. There should be no specific staining in the negative control. If staining occurs, it may indicate non-specific cross reactivity to cells or cellular components. Intact cells should be used for interpretation of staining results since necrotic or degenerated cells often stain non-specifically.

If the positive or negative control fails to demonstrate appropriate staining, any results with the test specimens should be considered invalid.

Patient Specimen

Patient specimens should be examined last. Positive staining intensity should be assessed within the context of any background staining of the negative reagent control. A negative result means that the RNA sequence in question was not detected, not necessarily that the sequence is absent in the cells assayed. The morphology of each sample should also be examined utilizing a hematoxylin and eosin stained section when interpreting any ISH result. The patient's morphologic findings and pertinent clinical data must be interpreted by a qualified pathologist.

LIMITATIONS

General Limitations

1. ISH is a multiple step methodology that requires specialized training in the selection of the appropriate reagents, specimen preparation, processing, preparation of the ISH slide, and interpretation of the 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 inherent irregularities within the tissue.
3. Excessive or incomplete counterstaining may compromise proper interpretation of results.
4. The clinical interpretation of staining must be evaluated within the context of clinical history, morphology, and other histopathological criteria. It is the responsibility of a qualified pathologist to be familiar with the 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 the review of the stained slides, and ensuring the adequacy of controls.
5. VENTANA reagents are provided at optimal dilution for use when the provided instructions are followed. Any deviation from recommended test procedures may invalidate expected results. Users must accept responsibility for interpretation of patient results when deviating from the recommended test procedures.
6. Due to variations in specimen processing it may be necessary to either increase or decrease the ISH protease treatment time. Such changes must be validated by the user. Users who deviate from recommended test procedures are responsible for interpretation of patient results under these circumstances.
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 tissues. Contact your local support representative with documented unexpected reactions.

SPECIFIC LIMITATIONS

1. This product cannot be reliably used to detect Lambda light chain mRNA in B-cells or B-cell neoplasms.
2. Excessive decalcification of bone/bone marrow samples can lead to degradation of mRNA. Therefore, in the case of a negative result, it is important to verify the integrity of the mRNA with a positive control probe, such as RNA Positive Control Probe.
3. When using fluorescein-labeled probes and the VENTANA ISH iVIEW Blue Detection Kit, cytoplasmic and/or nuclear staining in epithelial cells of gastrointestinal tissue may be observed. Use of the Negative Control Probe is required to detect this staining.
4. All assays might not be registered on every instrument. Please contact your local Roche representative for more information.

PERFORMANCE CHARACTERISTICS

ANALYTICAL PERFORMANCE

The performance of the INFORM Cytoplasmic Lambda mRNA Probe was evaluated through sensitivity, specificity, and precision studies. All staining was performed using the INFORM Cytoplasmic Lambda mRNA Probe protocol as noted in Table 4 on a BenchMark IHC/ISH instrument unless otherwise specified.

Sensitivity and Specificity

Table 4. Sensitivity/Specificity of INFORM Cytoplasmic Lambda mRNA Probe was determined by testing FFPE normal tissues.

Tissue	# positive / total cases	Tissue	# positive / total cases
Cerebrum[a]	0/3	Stomach[a]	0/3
Cerebellum	0/3	Small intestine[a]	0/3
Adrenal gland[a]	0/3	Colon[a]	0/3
Ovary	0/3	Appendix[a]	0/3
Pancreas	0/3	Liver[a]	0/3
Lymph node[a]	7/7	Salivary gland[a]	0/3
Parathyroid gland[a]	0/3	Pharynx[a]	0/3
Pituitary gland[a]	0/3	Kidney	0/3
Testis	0/3	Prostate[a]	0/3
Thyroid	0/3	Bladder[a]	0/3
Breast[a]	0/3	Endometrium[a]	0/3
Spleen[a]	3/3	Cervix[a]	0/3
Tonsil[a]	78/78	Skeletal muscle	0/3
Thymus[a]	0/3	Skin[a]	0/3
Bone marrow	2/7	Nerve	0/3
Lung	0/3	Mesothelium	0/3
Heart	0/3	Soft tissue[a]	0/3
Esophagus[a]	0/3		

[a] Infiltrating Plasma cells staining.

Table 5. Sensitivity/Specificity of INFORM Cytoplasmic Lambda mRNA Probe was determined by testing a variety of FFPE neoplastic tissues.

Pathology	# positive / total cases
Glioblastoma (Cerebrum)	0/1
Meningioma (Cerebrum)	0/1
Ependymoma (Cerebellum)	0/1
Oligodendroglioma (Cerebellum)	0/1
Adenocarcinoma (Head and neck)	0/1
Squamous cell carcinoma (Head and neck)	0/1
Adenoma (Adrenal gland)	0/1
Pheochromocytoma (Adrenal gland)	0/1
Granulosa cell tumor (Ovary)	0/1
Serous carcinoma (Ovary)	0/1
Teratoma (Ovary)	0/1
Neuroendocrine neoplasm (Pancreas)	0/1
Ductal adenocarcinoma (Pancreas)	0/1
Embryonal carcinoma (Testis)	0/1
Seminoma (Testis)	0/1
Follicular carcinoma (Thyroid)	0/1
Papillary carcinoma (Thyroid)	0/1
Ductal carcinoma in situ (DCIS) (Breast)	0/1
Invasive ductal carcinoma (Breast)	0/1
Invasive lobular carcinoma (Breast)	0/1
Ewing sarcoma (Bone marrow)	0/1
Adenocarcinoma (Lung)	0/1
Squamous cell carcinoma (Lung)	0/1
Small cell carcinoma (Lung)	0/1
Myxoma (Heart)	0/1
Adenocarcinoma (Esophagus)	0/1
Squamous cell carcinoma (Esophagus)	0/1
Adenocarcinoma (Stomach)	0/1
Gastrointestinal stromal tumor (GIST) (Stomach)	0/1
Adenocarcinoma (Small Intestine)	0/1
Gastrointestinal stromal tumor (GIST) (Small Intestine)	0/1
Adenocarcinoma (Colon)	0/1
Adenosquamous carcinoma (Colon)	0/1
Carcinoid (Appendix)	0/1
Cholangiocarcinoma (Liver)	0/1
Hepatocellular carcinoma (HCC) (Liver)	0/1
Pleomorphic adenoma (Salivary Gland)	0/1
Papillary renal adenoma (Kidney)	0/1
Renal cell carcinoma (Kidney)	0/1
Adenocarcinoma (Prostate)	0/2
Clear cell carcinoma (Uterus)	0/1
Endometrioid carcinoma (Uterus)	0/1
Leiomyoma (Uterus)	0/1
Leiomyosarcoma (Uterus)	0/1
Squamous cell carcinoma (Cervix)	0/1
Adenocarcinoma (Cervix)	0/1
Alveolar rhabdomyosarcoma (Muscle)	0/1
Basal cell carcinoma (Skin)	0/1
Squamous cell carcinoma (Skin)	0/1
Melanoma (Skin)	0/1
Neurofibrosarcoma (Peripheral nerve)	0/1
Schwannoma (Peripheral nerve)	0/1
Mesothelioma (Soft tissue)	0/1

Pathology	# positive / total cases
Solitary fibrous tumor (Soft tissue)	0/1
Angiosarcoma (Soft tissue)	0/1
Liposarcoma (Soft tissue)	0/1
Plasma cell myeloma[a,b]	9/18
Hodgkin lymphoma	0/11
Anaplastic large cell lymphoma (ALCL)	0/1
T-cell lymphoma, NOS	0/8
Burkitt lymphoma (Nose)	0/1
Follicular lymphoma	0/4
Diffuse large B-cell lymphoma (DLBCL)	0/9
Squamous cell carcinoma (Bladder)	0/1
Urothelial carcinoma (Bladder)	0/1

[a] Myeloma Restriction Status: 7/18 were Kappa restricted, 9/18 were Lambda restricted, 2/18 were negative for both.

[b] One myeloma case is from cerebrum.

Precision

Precision studies for INFORM Cytoplasmic Lambda mRNA Probe were completed to demonstrate:

- Within-run and Inter-run between-day precision on a BenchMark ULTRA instrument.
- Between-instrument intermediate precision on a BenchMark XT and BenchMark ULTRA instrument.
- Between-platform intermediate precision between the BenchMark XT and BenchMark ULTRA instrument.

Precision on the BenchMark ULTRA PLUS instrument was demonstrated using representative assays. Studies included Within-run Repeatability, Between-day and Between-run Intermediate Precision. All studies met their acceptance criteria.

CLINICAL PERFORMANCE

Clinical performance data relevant to the intended purpose of INFORM Cytoplasmic Lambda mRNA Probe were assessed by systematic review of the literature. The data gathered support the use of the device in accordance with its intended purpose.

TROUBLESHOOTING

Table 6. Troubleshooting solutions.

Issue	Solution
Positive control is negative.	Check that the slide has the proper barcode label.
Positive control is negative or exhibits weaker staining than expected.	Check other positive controls stained on the same staining run to determine if the failure is due to the control slide or reagents used. Positive control specimens are recommended for potential troubleshooting for each run.
Specimen staining is weak or absent.	Specimens may have been improperly collected, fixed, or stored. See the Specimen Preparation section. Check the reagent dispenser priming chamber or meniscus for foreign materials or particulates, such as fibers or precipitates. If the dispenser is blocked, do not use the dispenser and contact your local support representative. Otherwise, re-prime the dispenser by aiming the dispenser over a waste container, removing the nozzle cap, and pressing down on the top of the dispenser.
Tissue washes off slides	Ensure that positively-charged slides are used.
Sections thicker than 4 µm exhibit nuclear bubbling due to excess paraffin.	Select the "extended deparaffinization" option in the staining procedure. (Note: This option is available only for the BenchMark ULTRA instrument protocol.)
Tissue and glass slides exhibit excessive blue staining	Select the "extended deparaffinization" option in the staining procedure for BenchMark ULTRA instrument, or perform offline deparaffinization.

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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 elabdoc.roche.com/symbols for more information).

GTIN	Global Trade Item Number
Rx only	For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

REVISION HISTORY

Rev	Updates
F	Updates to Warnings and Precautions section. Updated to current template.

INTELLECTUAL PROPERTY

For USA: Rx only

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