

ultraView Universal DAB Detection Kit

REF 760-500

05269806001

IVD  250

INTENDED USE

ultraView Universal DAB Detection Kit is an indirect, biotin-free system for detecting mouse IgG, mouse IgM and rabbit primary antibodies. The kit is intended to identify targets by immunohistochemistry in sections of formalin-fixed, paraffin-embedded tissue, or frozen tissue, that are stained on the 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

Immunohistochemistry (IHC) is a technique used in laboratories for diagnostic purposes. IHC uses specific primary antibodies to localize and bind to antigens in fixed or frozen tissue sections. The binding of the antibody to the antigen is visualized with an indirect detection method. The most common techniques for indirect methods use a secondary antibody directed against the species of primary antibody and an enzyme with a corresponding substrate-chromogen system. This combination results in a colored precipitate at the site of specific antibody binding. The *ultraView* Universal DAB Detection Kit uses an indirect method to visualize specific antibodies bound to antigens by depositing a brown colored precipitate.

PRINCIPLE OF THE PROCEDURE

The *ultraView* Universal DAB Detection Kit detects specific mouse and rabbit primary antibodies bound to an antigen in formalin-fixed, paraffin-embedded (FFPE) tissue sections, or in frozen tissue sections. The specific antibody is located by a cocktail of enzyme labeled secondary antibodies. The complex is then visualized with hydrogen peroxide substrate and 3,3'-diaminobenzidine tetrahydrochloride (DAB) chromogen, which produces a brown precipitate that is readily observed 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.¹ Results are interpreted using a light microscope and aid in the differential diagnosis of pathophysiological processes, which may or may not be associated with a particular antigen.

For more detailed information on instrument operation, refer to the appropriate User Guide. Figure 1 illustrates the indirect detection method.

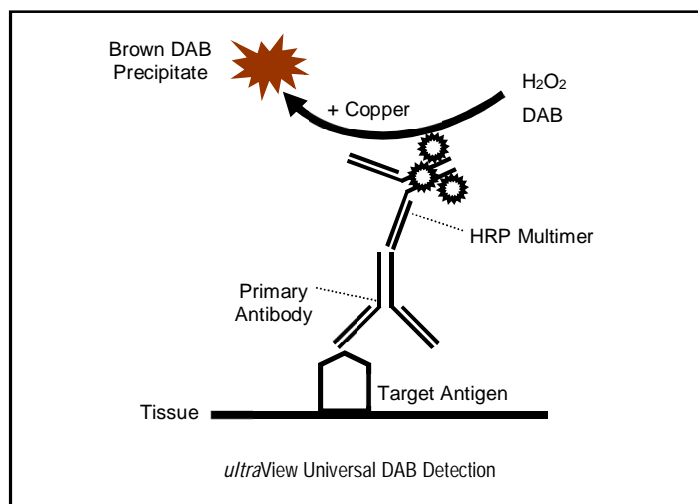


Figure 1. *ultraView* Universal DAB Detection Kit Reaction

MATERIAL AND METHODS

Materials Provided

ultraView Universal DAB Detection Kit contains sufficient reagent for 250 tests.

One 25 mL dispenser	<i>ultraView</i> Universal DAB Inhibitor contains 3% hydrogen peroxide solution.
One 25 mL dispenser	<i>ultraView</i> Universal HRP Multimer contains a cocktail of HRP labeled antibodies (goat anti-mouse IgG, goat anti-mouse IgM, and goat anti-rabbit) (approximately 55 µg/mL) in a buffer containing protein with ProClin 300, a preservative.
One 25 mL dispenser	<i>ultraView</i> Universal DAB Chromogen contains 0.2% w/v 3,3'-diaminobenzidine tetrahydrochloride in a proprietary stabilizer solution with a proprietary preservative.
One 25 mL dispenser	<i>ultraView</i> Universal DAB H ₂ O ₂ contains 0.04% hydrogen peroxide in a phosphate buffer solution.
One 25 mL dispenser	<i>ultraView</i> Universal DAB Copper contains copper sulfate (5 g/L) in an acetate buffer with proprietary preservative.

Reconstitution, Mixing, Dilution, Titration

The detection kit is optimized for use on BenchMark IHC/ISH instruments. No reconstitution, mixing, dilution, or titration of kit reagents is required. Further dilution may result in loss of staining.

Materials Required but Not Provided

Staining reagents, such as VENTANA primary antibodies 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 detection kit:

1. Primary antibody
2. Negative control reagent
3. Positive and negative tissue controls (consult antibody method sheets for recommended types)
4. Amplification Kit (Cat. No. 760-080 / 05266114001)
5. Protease 1 (Cat. No. 760-2018 / 05266688001)
6. Protease 2 (Cat. No. 760-2019 / 05266696001)
7. Protease 3 (Cat. No. 760-2020 / 05266718001)
8. Hematoxylin (Cat. No. 760-2021 / 05266726001)
9. Hematoxylin II (Cat. No. 790-2208 / 05277965001)
10. Bluing Reagent (Cat. No. 760-2037 / 05266769001)

11. Reaction Buffer Concentrate (10X) (Cat. No. 950-300 / 05353955001)
12. Cell Conditioning Solution 1 (CC1) (Cat. No. 950-124 / 05279801001)
13. Cell Conditioning Solution 2 (CC2) (Cat. No. 950-123 / 05279798001)
14. ULTRA Cell Conditioning Solution (ULTRA CC1) (Cat. No. 950-224 / 05424569001)
15. ULTRA Cell Conditioning Solution (ULTRA CC2) (Cat. No. 950-223 / 05424542001)
16. Antibody Diluent (Cat. No. 251-018 / 05261899001)
17. EZ Prep Concentrate (10X) (Cat. No. 950-102 / 05279771001)
18. LCS (Predilute) (Cat. No. 650-010 / 05264839001)
19. ULTRA LCS (Predilute) (Cat. No. 650-210 / 05424534001)
20. BenchMark IHC/ISH instrument
21. Microscope slides, positively charged
22. Coverslip and coverslip method sufficient to cover tissue
23. General purpose laboratory equipment

Storage and Stability

Upon receipt and when not in use, store at 2-8°C. Do not freeze. The user must validate any storage conditions other than those specified in the method sheet. This detection kit can be used immediately after removal from the refrigerator.

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

Every detection kit is expiration dated. When properly stored, the product is stable to the date indicated on the label. Do not use product beyond the expiration date for the prescribed storage method. There are no definitive signs to indicate instability of this product; therefore, positive and negative controls should be run simultaneously with unknown specimens. Your local support representative should be contacted immediately if there is an indication of reagent instability.

Specimen Collection and Preparation for Analysis

Routinely processed, FFPE tissues are suitable for use with *ultraView* Universal DAB Detection Kit and BenchMark IHC/ISH instruments (see Materials Required but Not Provided section). The recommended tissue fixative is 10% neutral buffered formalin (NBF).² Variable results may occur as a result of tissue section thickness, fixation type, incomplete prolonged fixation or special processes such as decalcification of bone marrow preparations.

Each section should be cut to the appropriate thickness for the primary antibody being used (see Method Sheet of antibody of interest) and placed on a positively charged glass microscope slide. Slides containing the tissue section should dry in an upright position for at least 15 minutes at room temperature to drain excess water from beneath the section before baking. The slides may be baked/heated for 1 hour in a 60°C ± 5°C oven, or air dried at 37°C up to 24 hours. Slide drying and heating is used to dry the tissue post slide mounting and to enhance tissue adhesion to the glass. Consult the primary antibody method sheet to identify heating limitations. Extended heating of the tissue might result in decreased antigen availability.

Properly fixed and embedded tissues expressing the antigen will remain stable if stored in a cool location (15-25°C). The Clinical Laboratory Improvement Act (CLIA) of 1988, 42CFR493.1259 (b) requires that "The laboratory must retain slides at least ten years from the date of examination and retain specimen blocks at least two years from date of examination." Each laboratory should validate the cut slide stability for their own procedures and environmental storage conditions.

Routinely processed, frozen tissues are also suitable for use with *ultraView* Universal DAB Detection Kit and BenchMark IHC/ISH instruments. The recommended tissue fixation is 10 minutes in cold acetone. Variable results may occur as a result of prolonged fixation or special processes such as decalcification of bone marrow preparations.


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. Warning: Possible carcinogen. The International Agency for Research on Cancer (IARC) and the US National Toxicology Program (NTP) have listed benzidine, a compound closely related to 3, 3'-diaminobenzidine tetrahydrochloride (DAB), as a known human carcinogen.
5. Do not use beyond the specified number of tests.

6. ProClin 300 solution is used as a preservative in this solution. 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.
7. 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.^{3,4}
8. Take reasonable precautions when handling reagents. Avoid contact of reagents with eyes, skin, and mucous membranes. Use disposable gloves and wear suitable protective clothing when handling suspected carcinogens or toxic materials.
9. If reagents come in contact with sensitive areas, wash with copious amounts of water. Avoid inhalation of reagents.
10. 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.
11. Avoid microbial contamination of reagents as this may produce incorrect results.
12. For further information on the use of this device, refer to the BenchMark IHC/ISH instrument User Guide, and method sheets of all necessary components located at navifyportal.roche.com.
13. Consult local and/or state authorities to determine the recommended method of disposal.
14. Product safety labeling primarily follows EU GHS guidance. Safety data sheet available for professional user on request.
15. 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
	H317	May cause an allergic skin reaction.
	H319	Causes serious eye irritation.
	H350	May cause cancer.
	H412	Harmful to aquatic life with long lasting effects.
	P201	Obtain special instructions before use.
	P261	Avoid breathing mist or vapours.
	P273	Avoid release to the environment.
	P280	Wear protective gloves/ protective clothing/ eye protection/ face protection/ hearing protection.
	P308 + P313	IF exposed or concerned: Get medical advice/ attention.
	P333 + P313	If skin irritation or rash occurs: Get medical advice/ attention.

PROCEDURE

ultraView Universal DAB Detection Kit has been developed for use on BenchMark IHC/ISH instruments in combination with VENTANA primary antibodies and ancillaries. The parameters for the automated procedures can be displayed, printed and edited according to the procedure in the instrument User Guide. Other operating parameters for the instrument have been preset at the factory.

The procedures for staining on BenchMark IHC/ISH instruments are below. For more detailed instructions and additional protocol options refer to your User Guide. Whether a sample requires Cell Conditioning is antibody dependent. Please check the antibody method sheet for directions.

BenchMark IHC/ISH Instruments

1. Apply slide bar code label which corresponds to the protocol to be performed.
2. Load the primary antibody, appropriate detection kit dispensers, and required accessory reagent onto the reagent tray and place them on the instrument.
3. Check bulk fluids and empty waste.
4. Load the slides onto the instrument.
5. Start the staining run.
6. At the completion of the run, remove the slides from the instrument.
7. Proceed to Recommended Post-Instrument Processing Procedures.

Recommended Post-Instrument Processing Procedures

1. Wash slides in a mild dishwashing detergent to remove the coverslip solution.
2. Rinse slides thoroughly in distilled water to remove all detergent.
3. Dehydrate, clear, and coverslip with permanent mounting media.

QUALITY CONTROL PROCEDURE

Positive Tissue Control

A positive tissue control must be run with every staining procedure performed. Optimal laboratory practice is to include a positive control section on the same slide as the patient tissue. This practice helps to identify a failure to apply primary antibody or other critical reagent to the patient test slide. A tissue with weak positive staining is more suitable for optimal quality control. The positive staining tissue components are used to confirm that the 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.

Known positive tissue controls should be utilized only for monitoring the correct performance of processed tissues and test reagents, 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

The same tissue used for the positive tissue control may be used as the negative tissue control. The variety of cell types present in most tissue sections offers internal negative control sites, but this should be verified by the user. The components that do not stain should demonstrate the absence of specific staining, and provide an indication of background staining. If specific staining occurs in the negative tissue control sites, results with the patient specimens should be considered invalid.

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 method sheet. Identify and correct the problem, then repeat the patient samples.

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. The slide should be stained with Negative Control Mouse or Negative Control Rabbit, as appropriate. The diluent alone may be used as an alternative to the previously described negative reagent controls. The incubation period for the negative reagent control should equal the primary antibody incubation period.

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 a primary antibody or staining system in a diagnostic procedure, the specificity of the primary antibody should be verified by testing it on a series of tissues with known immunohistochemistry performance characteristics representing known positive and negative tissues (refer to the Positive Tissue Control section in the primary antibody method sheet and to the Quality Control recommendations of the College of American Pathologists Laboratory Accreditation Program, Anatomic Pathology Checklist,⁵ or the CLSI Approved Guideline⁶ or both documents). These quality control procedures should

be repeated for each new antibody lot, or whenever there is a change in assay parameters. Tissues listed in the Performance Characteristics section of the primary antibody are suitable for assay verification.

Interpretation of Results

The *ultraView* Universal DAB Detection Kit causes a brown colored reaction product to precipitate at the antigen sites localized by the primary antibody. A qualified pathologist who is experienced in immunohistochemical procedures must evaluate controls and qualify the stained product before interpreting results. Staining of negative controls must be noted first, and these results compared to the stained material to verify that the signal generated is not the result of nonspecific interactions.

Positive Tissue Control

The stained positive tissue control should be examined first to ascertain that all reagents are functioning properly. The presence of an appropriately colored reaction product within the target cells is indicative of positive reactivity. Depending on the incubation length and potency of the hematoxylin used, counterstaining will result in a pale to dark blue coloration of cell nuclei. Excessive or incomplete counterstaining may compromise proper interpretation of results.

If the positive tissue control fails to demonstrate 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. 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 sections from excessively formalin-fixed tissues. Intact cells should be used for interpretation of staining results. Necrotic or degenerated cells often stain nonspecifically.

Patient Tissue

Patient specimens should be examined last. Positive staining intensity should be assessed within the context of any non-specific background staining of the negative reagent control. As with any immunohistochemical test, a negative result means that the antigen in question was not detected, not that the antigen is absent in the cells or tissue assayed. If necessary, use a panel of antibodies to aid in the identification of false negative reactions. 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 morphological findings and pertinent clinical data must be interpreted by a qualified pathologist.

LIMITATIONS

General Limitations

1. IHC is a multiple step diagnostic process that requires specialized training in the selection of the appropriate reagents, tissue selections, 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 result from 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. It is the responsibility of a qualified pathologist to be familiar with the antibodies, reagents and methods used to interpret 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 antibodies and reagents are provided 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. 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.⁷ Contact your local support representative with documented unexpected reactions.
7. Tissues from persons infected with hepatitis B virus and containing hepatitis B surface antigen (HBsAg) may exhibit nonspecific staining with horseradish peroxidase.⁸
8. When used in blocking steps, normal sera from the same animal source as the secondary antisera may cause false negative or false positive results because of autoantibodies or natural antibodies.
9. As with any immunohistochemistry 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. Each step of the detection kit procedure has been optimized on BenchMark IHC/ISH instruments and is preset. Because of variation in tissue fixation and processing, it may be necessary to increase or decrease the primary antibody incubation time on individual specimens. Primary antibody incubation time depends on the degree of tissue fixation, and may range from 8 to 32 minutes. For further information on fixation variables, refer to "Immunohistochemistry Principles and Advances"⁹ or "Immunomicroscopy: A Diagnostic Tool for the Surgical Pathologist."¹⁰
2. The detection kit, in combination with VENTANA primary antibodies and accessories, detects antigen that survives routine formalin fixation, tissue processing, and sectioning.
3. This detection kit has been optimized for use with Reaction Buffer wash solution, primary antibodies, accessories, and BenchMark IHC/ISH instruments. The use of Reaction Buffer wash solution is important to the proper function of the detection kit. Users who deviate from recommended test procedures are responsible for interpretation of patient results under these circumstances.
4. This detection kit has been optimized for use with LCS (Predilute) or ULTRA LCS (Predilute). LCS is a prediluted coverslip solution used both as a barrier between aqueous reagents and the air as well as a reagent to remove paraffin from tissue samples during the deparaffinization process. The LCS barrier reduces evaporation and provides a stable aqueous environment for the IHC or in situ hybridization (ISH) reaction carried out on VENTANA instruments.
5. Incubation times and temperatures other than those specified may give erroneous results. The user must validate any such change.
6. All detection kits might not be registered on every instrument. Please contact your local Roche representative for more information.

PERFORMANCE CHARACTERISTICS

ANALYTICAL PERFORMANCE

The performance of the *ultraView* Universal DAB Detection Kit was evaluated through precision and other relevant studies. All staining was performed using the protocol as noted in the antibody method sheet on BenchMark IHC/ISH instruments unless otherwise specified.

Precision Studies

ultraView Universal DAB Detection Kit precision testing was performed by staining serial sections from 3 neutral buffered FFPE tissues using 3 primary antibodies, a mouse IgG (anti-Ki67) stained on breast carcinoma, a mouse IgM (anti-CD15) stained on a Hodgkin Lymphoma xenograft and a rabbit IgG (anti-S100) on a melanoma using BenchMark and BenchMark XT instruments. All primary antibodies were incubated for 16 minutes and slides counterstained using Hematoxylin II followed by Bluing Reagent. All slides stained with a primary antibody were compared against each other for staining appropriateness and intensity:

1. Within-run precision (same primary antibody stained on a platform compared) staining runs were performed one per day on 3 separate days using 2 different instruments: BenchMark and BenchMark XT instruments for a total of 6 staining runs. Within-run precision for the BenchMark XT instrument was 100% (30 of 30

slides per primary antibody per run, a total of 90 slides stained per antibody across the 3 runs) and 100% (20 of 20 slides per primary antibody per run, a total of 60 slides per antibody across 3 runs) for the BenchMark instrument).

2. Between-run precision was calculated based on the number of slides stained in 3 runs per instrument type. Staining runs were performed one per day on 3 separate days using 2 different instruments: BenchMark and BenchMark XT instruments. Between-run precision for the BenchMark XT instrument was 100% (90 of 90 slides, 30 slides for each primary antibody across 3 separate runs) and 100% (60 of 60 slides, 20 slides for each primary antibody across 3 separate runs for each platform) for the BenchMark instrument.
3. Between-instrument precision was calculated based on the number of slides stained in 6 runs across all instrument types. Staining runs were performed 1 per day on 3 separate days using 2 different instruments: BenchMark and BenchMark XT instruments. *ultraView* Universal DAB Detection Kit between-instrument precision is 100% (150 of 150 stained slides, evaluated slides included all 3 primary antibodies).

Multiple VENTANA primary antibodies have been developed with the *ultraView* Universal DAB Detection Kit. As part of the testing for those assays, the following performance characteristics were demonstrated for *ultraView* Universal DAB Detection Kit:

1. Within-run, Between-day, Between-instrument, and Between-platform precision on the BenchMark GX, BenchMark XT and BenchMark ULTRA instruments.
2. Sensitivity and specificity of staining across a range of normal and neoplastic tissue types and assay-specific target tissues
3. Precision on the BenchMark ULTRA PLUS instrument was demonstrated using representative assays. Studies included within run, between day and between instrument precision. All studies met their acceptance criteria

TROUBLESHOOTING

1. If the positive control exhibits weaker staining than expected, other positive controls run during the same instrument run should be checked to determine if it is because of the primary antibody or one of the common secondary reagents.
2. If the positive control is negative, it should be checked to ensure that the slide has the proper bar code label. If the slide is labeled properly, other positive controls run on the same instrument run should be checked to determine if it is because of the primary antibody or one of the common secondary reagents. Tissues may have been improperly collected, fixed, or deparaffinized. The proper procedure should be followed for collection, storage and fixation.
3. Incomplete paraffin removal could result in staining artifacts or no staining.
 - If all paraffin has not been removed from the slide, the staining run should be repeated using the extended deparaffinization option, if available.
 - Alternatively, a manual off-instrument deparaffinization can be performed. If the manual option is used, deselect online deparaffinization from the staining protocol prior to loading the slides on the instrument. Extra care should be taken to ensure slides do not dry out prior to the staining run.
4. If specific antibody staining is too intense, the run should be repeated with incubation time shortened by 4 minute intervals until the desired stain intensity is achieved.
5. If tissue sections wash off the slide, slides should be checked to ensure that they are positively charged.
6. For corrective action, refer to the Procedure section, the instrument User Guide or contact your local support representative.
7. If a reagent dispenser does not dispense fluid, check the 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. Refer to the associated inline dispenser method sheet associated with P/N 760-500 for information about proper use.

REFERENCES

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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.

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).



Global Trade Item Number



Unique Device Identifier



Indicates the entity importing the medical device into the European Union

REVISION HISTORY

Rev	Updates
K	<p>Updates to Warnings and Precautions, instruction for use and symbol reference links in the Warnings and Precautions and Symbol sections.</p> <p>Updates to applicable References</p>

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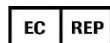
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