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P40

RABBIT ANTI-P40 MONOCLONAL ANTIBODY (Clone ZR8)

1 CATALOG REFERENCES AND PRESENTATIONS

The references and presentations available for this product are described in the following table:

Table 1. References and presentation

Reference		Presentation[1]
MAD-000686	Q	1 mL
	QD-3	3 mL
	QD-7	7 mL
	QD-12	12 mL
	QD-3/V	20 tests
	QD/V	45 tests
	QDS-1	7 mL
	QDS-2	14 mL
	QDS-3	28 mL

[1] All product presentations are in Ready-to-Use format, except for the reference ending in Q, which is supplied in Concentrate format. References ending in S for use in the VitroStainer 42. The use of the product in other immunostainers must be validated locally according to the instrument and the existing conditions in each laboratory. Not to be used for western blotting and flow cytometry techniques.

2 INTENDED PURPOSE OF THE PRODUCT

P40 is a primary antiserum for immunohistology for professional use, for the qualitative determination of P40 antigen to *in vitro* diagnostics in the laboratory by automated and manual immunohistochemistry, on paraffin-embedded tissue in neoplasms and in all other clinicopathological and physiological situations where identification is required. The product is intended to be used as an aid for screening, diagnosis, staging or monitoring of cancer for people of any age with suspected neoplasms or other clinicopathological and physiological situations requiring the analysis of P40 molecule expression.

This antibody is essential for the identification of squamous cell, urothelial and myoepithelial differentiation; used for the diagnosis of squamous cell carcinoma of any location, being among the markers of the panel recommended for the subtyping of non-small cell lung carcinoma. The clinical interpretation of any staining or lack thereof should be supplemented by morphologic studies using appropriate controls and should be evaluated by a qualified pathologist in the context of the patient's medical history and other appropriate diagnostic tests.

3 OTHER POSSIBLE APPLICATIONS OF THE PRODUCT

This antibody has also been reported that P40 is also of interest in the characterization of tumors and carcinomas of the head and neck in nasal cavity/nasopharynx (Nasopharyngeal carcinoma and NUT carcinoma) and in salivary glands (Adenoid cystic carcinoma, Myoepithelial carcinoma, Basal cell adenoma and basal cell carcinoma, Oncocytoma, Myoepithelioma, Epithelial-myoepithelial carcinoma, Pleomorphic adenoma and Mucoepidermoid adenoma), of thymus (Thymoma and Thymic carcinoma); and of the Urothelial carcinoma. Nevertheless, this antibody has not been validated for its use in these pathologies.

4 DESCRIPTION OF THE MOLECULE IDENTIFIED BY THE PRODUCT

p63 protein (p63) is a nuclear protein, a transcription factor. The p63 gene is located at chromosome 3q27-29 and belongs to the p53 gene family. p63 plays a critical role in the growth and development of many epithelial organs. p63 is confined to basal cells of squamous epithelia (including epidermis and hair follicles) and urothelium, as well as basal cells/myoepithelial cells in breast, sweat glands, salivary glands, and prostate. p63 exists in two isoforms: TAp63, which is a p53 like tumour suppressor, and ΔNp63, which is an oncogene. P40 (originally an antibody against the ΔN domain of p63, but now used as a synonym) is the predominant p63 isotype in basal/progenitor cells [1]

Gene summary: This gene encodes a member of the p53 family of transcription factors. The functional domains of p53 family proteins include an N-terminal transactivation domain, a central DNA-binding domain and an oligomerization domain. Alternative splicing of this gene and the use of alternative promoters results in multiple transcript variants encoding different isoforms that vary in their functional properties. These isoforms function during skin development and maintenance, adult stem/progenitor cell regulation, heart development and premature aging. Some isoforms have been found to protect the germline by eliminating oocytes or testicular germ cells that have suffered DNA damage. Mutations in this gene are associated with ectodermal dysplasia, and cleft lip/palate syndrome 3 (EEC3); split-hand/foot malformation 4 (SHFM4); ankyloblepharon-ectodermal defects-cleft lip/palate; ADULT syndrome (acro-dermato-ungual-lacrimal-tooth); limb-mammary syndrome; Rap-Hodgkin syndrome (RHS); and orofacial cleft 8 [2]

Protein function: Acts as a sequence specific DNA binding transcriptional activator or repressor. The isoforms contain a varying set of transactivation and auto-regulating transactivation inhibiting domains thus showing an isoform specific activity. Isoform 2 activates RIPK4 transcription. May be required in conjunction with TP73/p73 for initiation of p53/TP53 dependent apoptosis in response to genotoxic insults and the presence of activated oncogenes. Involved in Notch signaling by probably inducing JAG1 and JAG2. Plays a role in the regulation of epithelial morphogenesis. The ratio of DeltaN-type and TA*-type isoforms may govern the maintenance of epithelial stem cell compartments and regulate the initiation of epithelial stratification from the undifferentiated embryonal ectoderm. Required for limb formation from the apical ectodermal ridge. Activates transcription of the p21 promoter [3].

5 EXPRESSION IN NORMAL TISSUES

The expression of the P40 in normal tissues primarily involves epithelial cells, where it plays a crucial role in the maintenance of epithelial integrity and differentiation. P40 expression is notably prominent in various stratified epithelia, such as the epidermis, oral mucosa, and squamous epithelium of the respiratory and gastrointestinal tracts (1–3). Additionally, it has been observed in basal cells of certain glandular epithelia (4). These findings suggest that P40 expression is characteristic of tissues with squamous differentiation and is involved in regulating epithelial cell proliferation and differentiation.

6 DIAGNOSTIC, PROGNOSTIC AND PREDICTIVE AID APPLICATIONS

6.1 Diagnostic aid, monitoring and staging

The P40 protein is expressed in a nuclear pattern in myoepithelia, urothelia and is present in the basal layer of squamous epithelium. P40 is a marker for squamous cell carcinomas has been used as the primary marker for

[1] https://www.nordiqc.org/epitope.php?id=10
[2] https://www.proteinatlas.org/ENSG00000073282-TP63
[3] https://www.proteinatlas.org/ENSG00000073282-TP63

identifying squamous cell carcinoma because of its high sensitivity, which approaches 100%. In fact, it is part of the immunohistochemical panel recommended for subtyping non-small cell lung carcinoma in diagnostic incisional biopsy, in order to optimize the material of the same given the importance of molecular markers for the personalization of the treatment of this type of cancer (5,6).

P40 is also used for the diagnosis of urothelial carcinoma, thymic neoplasms such as thymoma and thymic carcinoma, and nasal cavity tumors such as nasopharyngeal carcinoma and NUT carcinoma (7).

Salivary gland tumors are a heterogeneous group of neoplasms and show varied clinical and histologic profiles; salivary neoplasms often show an extremely diverse morphology and significant histologic patterns that necessitate more efforts to make the diagnosis. The histologic diversity of salivary gland tumors is mainly due to the presence of multiple tumor cell differentiation like myoepithelial, basal, and ductal cells, which makes them a diagnostically complex neoplasm. An immunohistochemical panel containing P40 is a useful tool to differentiate salivary gland tumors containing myoepithelial cells, such as pleomorphic adenoma and adenoid cystic carcinoma among others (8–11).

6.1.1 Possible indications of prognostic and predictive use

In relation to prognosis, high-intensity P40 immunostaining has been significantly associated with reduced survival of patients with muscle-invasive urothelial carcinoma; Leivo et al. present results suggesting that, while GATA-3 and uroplakin II may be more useful in the diagnosis of urothelial carcinoma metastases, P40 may also be suitable as a prognostic marker (7).

Xu et al. have shown that using a score based on the use of several immunohistochemical markers, including P40, is significantly associated with prognosis in patients with head and neck squamous cell carcinoma. They suggest that a nomogram that integrates immunohistochemical scores and multiple clinical factors can be a powerful tool for evaluating clinical outcomes in patients with head and neck squamous cell carcinoma (12).

6.2 Clinical specificity and sensitivity

In the pursuit of clinical validation, we deemed it appropriate to rely on a comparative analysis of the positive cases detected using our product against those documented in the literature for similar products. This approach is grounded in the following considerations:

The P40 (ZR8) enjoys a well-established reputation as a diagnostic marker, bolstered by robust support in the existing literature.

The P40 (ZR8) serves as a diagnostic tool that primarily leans on qualitative assessment rather than quantitative measures. It is largely contingent on the clinical judgment of pathologists, who, in conjunction with other histopathological data and additional markers, arrive at a diagnosis.

The P40 product is a monoclonal antibody with limited diagnostic potential but high specificity, and its immunohistochemical interpretation could be dependent of performed in the morphologic context of the lesion analyzed and in conjunction with other immunohistochemical markers. P40 antibody has proven its utility in the diagnosis of squamous cell carcinoma of any site.

In relation to the use of the P40 antibody as a diagnostic support and considering that its high specificity is widely recognized in the literature (it can be positive in only a very small histological types of malignant neoplasms), with high sensitivity, to evaluate the metrological traceability of the antibody we show the comparative results between the literature and the P40 product from VITRO, S.A. in the short list of cases include in adnexal table where the P40 antibody shows sensitivity of 94% as well as remarkable specificity with intense-moderate staining in the presence of a concordant histology.

The sensitivity of VITRO, S.A. data has been compared to the sensitivity value found in the literature.

Table 2. Comparison of VITRO, S.A.'s sensitivity value with data obtained in literature.

P40	Sensitivity Literature	Specificity Literature	Sensitivity in the clinical series of VITRO, S.A.
Squamous cell carcinoma (13–16)	77-98%	High in the proper histological context	94% (47 cases out of 50)

Test results should be evaluated in conjunction with other diagnostic technologies, patient's medical history and other findings.

Since the performance characteristics may vary with pre analytical conditions, sample handling and storage, reagents, it is recommended that each laboratory establish its own verification of the results.

7 PRODUCT DESCRIPTION

7.1 Composition

Ready-to-use RABBIT anti-P40 monoclonal antibody supplied in liquid format in an pH7.6 buffer containing the stabilizing protein. Although it is not a sterile product, microbiological contamination is controlled, although not monitored since the solution contains sodium azide as a bacteriostatic and bactericidal agent. This additive improves device performance without affecting measurement results. The amount of active antibody in the sample is 1 µg/ml.

The antibody is also available in concentrated format supplied in liquid form in a pH7.6 buffer containing stabilizing protein with added sodium azide as a bacteriostatic and bactericidal agent.

7.2 Clone

ZR8 (identified in the batch field of the product label)

7.3 Immunostaining pattern (samples and controls)

Nuclear

7.4 Immunogen

Synthetic polypeptide corresponding to the N-terminal moiety of human P40 protein.

7.5 Immunoglobulin source and isotype

Rabbit / IgG.

7.6 Intended Use

Professional laboratory use. In vitro diagnosis in humans.

7.7 Application

Immunohistochemical determinations on paraffin-embedded tissue.

7.8 Storage conditions

Fridge or cold store between 2 and 8 °C. Do not freeze.

7.9 Validity period

The product, if preserved in the established storage conditions, can be used up to the expiration date indicated on the label. If the reagent has been stored in different conditions than the ones specified, the user must make sure that it works correctly, being aware that the product warranty is no longer valid.

The reagent, once opened and in use, is stable up to 19 months and at most up to the expiration date indicated on the label if stored and used according to the manufacturer's recommendations.

7.10 Special instructions for manipulation

This reagent is specially designed for its use in the immunostainer VitroStainer 42, although the use of other automated immunostainers and manual procedures is possible as long as the reagent is validated locally according to the conditions existing in each laboratory.

For a concentrated format, the recommended dilution is 1:50 (it has been validated with the immunodetection system Master Polymer Plus Detection System-Peroxidase ref. MAD-000237QK). The recommended buffer for this product is MAD-004048R Antibody diluent from VITRO, S.A.

8 CALIBRATORS AND CONTROL MATERIALS RECOMMENDED FOR LABORATORY USE DURING IHC TEST

8.1 Internal positive control

Any of the normal cells described in section 5 when present in the test sample.

8.2 External positive control

Tissue section from normal amygdala with previous expression of this marker, ideally placed on the same slide as the test specimen.

8.3 Negative control

Preparation homologous to the test sample incubated with a non-specific isotype antibody for P40.

8.4 External quality controls

It is highly recommended that each laboratory establishes an external quality assurance control system for its immunohistochemical procedures through recognized intercomparison programs.

9 SAMPLE TYPES

Paraffin-embedded tissue sections at 4 microns thickness and mounted on special slides for immunohistochemistry. These sections do not require any special conditions for sample collection, handling and preparation other than the standards established in each laboratory, except in the case of suspected prion infection where appropriate preventive measures should be taken (see also section 14 Warnings and Precautions). In buffered formalin-fixed samples the determination is direct and universal. If the sample has been processed in other fixatives or if it is frozen material, a local validation of the procedure must be carried out beforehand. Product intended for people of any age range requiring the analysis of P40 molecule expression levels by immunohistochemistry techniques on formalin-fixed and paraffin-embedded tissue.

10 ANTIGEN RETRIEVAL

The sections must be subjected to heat-induced antigen retrieval according to the standard procedure of each laboratory. In short, the process includes deparaffining of the sections, heat-induced antigen retrieval and subsequent washes in buffer. It is highly recommended that the samples used for immunostaining have been freshly sectioned on the microtome (freshly cut or cut the day before the test is performed).

In order to know the technical conditions of this antibody on VitroStainer 42, contact your authorized Supplier/Distributor.

Although this antibody clone has been successfully used in antigen retrieval systems and other immunostainers than those mentioned above, its use in them requires prior validation.

11 ANALYTICAL PRINCIPLE OF THE METHOD AND PERFORMANCE CHARACTERISTICS

Antigen detection on tissues and cells using a multistep immunohistochemical procedure that at least includes incubation with the primary antibody, incubation with an enzymatically labeled bridging immune reagent (ideally multispecies and polymeric in structure), revealing of such activity by a colorimetric reaction, contrast staining with hematoxylin and corresponding washes between steps.

11.1 Analytical sensitivity and specificity

This antibody is specific for the human P40 and does not cross-react with other molecules. Likewise, the concentration at which it is supplied, determined by dilution of the culture supernatant, is suitable for immunohistochemical determination by kits using peroxidase or alkaline phosphatase polymers.

11.1.1 Analytical sensitivity

Analytical sensitivity was carried out with both manual and automated procedures on VitroStainer 42 instrument, to confirm the optimal dilution and time of incubation of the P40 Antibody assuring the good results under the final selected conditions. Results showed that optimal results on target cells without nonspecific labeling or background noise were obtained.

11.1.2 Analytical Specificity (Interference / Cross-reactivity)

Analytical specificity testing was performed in order to find interference substances or cross reactivity results.

- **Interference analysis:** Analysis substances used during the process which demonstrated a loss of staining activity and thus should not be used in conjunction with the processing of samples to be stained using P40 Antibody. The only known interference comes from alcohol containing fixatives, which demonstrated a loss of staining activity and thus should not be used in conjunction with the processing of samples to be stained using this product (17)
- **Cross reactivity:** The results obtained under the optimum conditions defined for the test are as follows:

Table 3. Cross reactivity results. Positive controls containing internal negative controls

Tissue	Positive	Negative
Amygdala	P40 is present in certain immune cells, such as microglia and possibly astrocytes.	Negative expression in neurons.
Skin	P40 is notably present in immune cells, such as lymphocytes and dendritic cells.	Negative expression in non-immune cells like epithelial cells.
Result	Optimal	Optimal

All the results were analyzed by a pathologist.

Final optimal results were accorded with the acceptance criteria.

11.2 Precision

The determination of P40 by this monoclonal antibody is reproducible if the developing kits recommended in the instructions for use are used.

11.2.1 Repeatability

The repeatability of the method was analyzed using positive tonsil controls previously tested with positive results. The tests were performed by the same operator, at a single location and with the same instrument, and using the same batches of reagents on three consecutive days. All results were analyzed by a pathologist. It is concluded that the technique is 100% repeatable on all 3 days.

11.2.2 Reproducibility

The reproducibility of the method was analyzed using the automated method and optimized conditions for this marker by processing the same positive tonsil controls but performing the tests with different lots of reagents, operators and equipment. It is concluded that the technique is 100% reproducible.

11.3 Limits of detection

As there are currently used no routinely applicable quantitative procedures to ensure limits of detection on these qualitative non-linear products, as an alternative to these methods and to ensure dilution of the antibody, the following three internal procedures have been used:

1. Progressive dilution of the antibody in VitroStainer 42, on control tissues, confirming for experience the dilution located in the median between excessive staining not acceptable for diagnosis and weakly positive, which does not ensure the exclusion of false negatives.
2. External validation of the selected dilution in several clinical series of reference laboratories and in the NordiQC Quality Control and Quality Assurance Centers in immunohistochemistry of the Spanish Society of Anatomic Pathology (SEAP).
3. Results: The NordiQC Quality Control and Quality Assurance Centers in immunohistochemistry of the Spanish Society of Anatomic Pathology Reports can be requested to VITRO.
4. Review of the dilution used in the scientific literature for this same type of clone and/or antibody evaluated. See references (18,19)

11.4 Measurement range

Not Applicable. The immunohistochemical process is not a quantitative method, it is a qualitative one where the marking obtained is interpreted as positive or negative complemented with the corresponding morphological and histological studies of each lesion and the appropriate controls.

12 PRODUCT LIMITATIONS

1. Not recommended for Western-blotting and flow cytometry techniques.

2. The use on frozen tissue has not been evaluated.

3. This antibody is intended for in vitro diagnostic (IVD) use by qualified laboratories only.

4. Test results should be evaluated in conjunction with other diagnostic technologies, patient's medical history and other findings.

5. Since the performance characteristics may vary with pre analytical conditions, sample handling and storage, reagents, it is recommended that each laboratory establish its own verification of the results.

6. Each laboratory must define its own use ratings for the product following the manufacturer's instructions and calibrate the equipment where they are to be used.

7. Due to inevitable variability in immunohistochemical procedures and variables, appropriate positive and negative controls must be used and documented, and the results are to be interpreted by a qualified pathologist.

8. Prediluted antibodies, which are provided in a ready- to-use optimally diluted format, must be used explicitly as instructed. Improper handling and processing of tissue samples and reagents, and any deviation from the recommended procedures outlined herein, may compromise the validity and/or analysis of the results.

9. If concentrated antibodies are provided in a format that requires dilution in the optimized buffer, in the context of appropriate validation by the user, any diluent different than that specified in the package insert must also be validated by the user to ensure proper compatibility with the antibody. Once diluted, any deviation from the recommended procedures outlined herein may compromise the validity and/or analysis of the results.

10. The potential for unexpected results in patient tissue specimens cannot be eliminated due to inherent biological variability in the expression of certain antigens.

11.The potential for false positive results in patient tissue specimens cannot be eliminated due to the possibility of non-immunological binding of substrate reaction products or proteins. False positive results may also occur subject to the type of immunostaining technique used, or due to the activity of pseudoperoxidase, endogenous peroxidase, or endogenous biotin.

12. Due to the effect of autoantibodies or natural antibodies, normal sera from an animal source the same as the secondary antisera may result in false negative or false positive results when used in blocking steps.

13 EQUIPMENT AND PRODUCTS REQUIRED

13.1 Supplied with the reagent

Besides the antibody the product does not include any additional reagents needed.

13.2 Not supplied with the reagent

Reagents, materials and equipment necessary for the immunohistochemistry technique are available in the VITRO, S.A. product catalog, but not supplied with the device:

- VitroStainer 42
- Pretreatment Kit
- Detection system
- Silane-treated slide
- TBS buffer – Tween 20
- Optical microscope and/or a digital scanner of histological slides

All the immunostaining process of the sections and the codes of the system (which allows the online recognition of the reagent and the slides undergoing a study) are programmed in the immunostainer's software. Therefore, when a laboratory implements this analysis procedure for the first time, it is essential to ensure that the information accumulated in the instrument is correctly programmed. Contact your Authorized Supplier / Distributor if required.

Keep in mind that the optimal working conditions can vary depending on the type of tissue and that, in any case, they must be individually established for each laboratory. In general, and to optimize the process, it is recommended to use the different amplification, development and counterstaining products in form of kits manufactured by VITRO, S.A., in the immunostainer, as well as the specific buffers and consumables for these instruments.

This antibody has been optimized and validated with the detection system commercialized by VITRO, S.A. (MAD-000237QK, QP, QKVS) in the automated VitroStainer 42 although the product can work well with any other polymer-based detection system and with other automated systems or manual immunostaining procedures. If the product is to be used with detection systems and systems other than those recommended above, it is necessary to carry out a prior validation process in each laboratory.

14 WARNINGS AND PRECAUTIONS

- **Read the instructions for use before using this product.** In case of atypical or unexpected results, please contact your Authorized Supplier/Distributor.
- **Professional Use.** When the product is used as an aid to diagnosis, or to establish parameters of prognostic or predictive value about neoplasms, it should only be handled by trained users and in authorized laboratories and strictly following the instructions contained in this brochure.
- **Optimization and interpretation.** It should be borne in mind that the ultimate responsibility for the optimization and interpretation of the immunostaining performed lies with the physician and technicians who use it and that, likewise, this reagent is only a tool for the interpretation of the morphological findings of each case in conjunction with other diagnostic and prognostic tests and the pertinent clinical data of the patient.
- **Use:**
  - For its handling in research, the presentation as a concentrated antibody is more suitable, which allows investigating the most appropriate antibody dilution and conditions of use in each case.
  - The reagent only works properly with a reagent chain suitable for amplification and development, so its use with other systems than the recommended one should be subject to close review and/or eventual validation in each laboratory.
  - Except for the requirement that the special slides on which the sections to be treated with this reagent are mounted (which are electrostatically charged) must be kept away from sources of radiation, and those relating to exposure to high temperatures or excessive light, there are no other external or environmental influences on the reagent or interference of the reagent with other investigations or treatments to be performed on the patient.
- **Serious incident.** Any serious incident related to the use of this product that involves or may involve a serious deterioration, temporary or permanent, of the state of health of a patient, user or other person, or even death, or a serious threat to public health, must be reported as soon as possible to the manufacturer by e-mail at regulatory@vitro.bio and to the competent Health Authority of the EU member state where the user or patient is established. Incidents caused by misuse of the product or by the use of the product beyond the useful life established on its labeling will be the responsibility of the user.
- **The safety and disposal precautions are described in the Safety Data Sheet of this product.** This product is only intended for professional laboratory purposes, and it is not intended for pharmacological, home or

any other type of use. The current version of the Safety Data Sheet of this product can be downloaded in the web page www.vitro.bio or requested at regulatory@vitro.bio.

- **Summary of Safety and Performance (SSP):** The Summary of Safety and Performance (SSP) of this product will be available on EUDAMED database (subject to EUDAMED availability). This summary is also available on request by e-mail at regulatory@vitro.bio.

- **Recommendations for the Safe Handling of Samples Suspected of Containing Prions:**

  The following protective measures are recommended for professional personnel handling immunohistochemistry (IHC) samples suspected of containing prions:

  - Personal protective equipment (PPE): full PPE should be worn, including a mask (preferably FFP2 or higher), protective goggles or face shield, head cover, and shoe covers.
  - Precautions during microtome sectioning: use disposable blades and avoid the use of aerosols or compressed air to clean the microtome area.
  - Surface and equipment decontamination: disinfect with sodium hydroxide (NaOH) 1N or sodium hypochlorite at 2%.
  - Waste management: all disposable materials must be discarded as special biological risk waste, in accordance with the applicable national regulations on hazardous healthcare waste.

- **Waste disposal:** The handling of waste generated by the use of the products commercialized by VITRO S.A. must be performed according to the applicable law in the country in which these products are being used. As reference, the following table indicates the classification of waste generated by this kit according to the European Law, specifically according to the *European Commission Decision of December 18, 2014,* amending decision 2000/532/CE on the list of waste pursuant to Directive 2008/98/EC of the European Parliament and of the Council:

Table 4. Classification of waste generated by this kit according to the European Legislation. *ELW: *European Legislation of Waste*

POTENTIAL WASTE GENERATED AFTER USING THIS PRODUCT	ELW* CODE	TYPE OF WASTE ACCORDING TO ELW*
Container for reagents used classified as dangerous (according to the Safety Data Sheet).	150110	"Containers containing waste or contaminated by dangerous substances"
Aqueous liquid waste containing hazardous substances (not solvents).	161001	"Liquids generated from the use of automatic IHC/HIS instruments: - Waste deposit of immunostainers. - used PT-Module buffers"
Consumables material (tubes, tips, aluminum foil, etc.). Any element that has been in contact with tissue samples.	180103	"Waste whose collection and disposal is subject to special requirements in order to prevent infection"
Liquids containing solvents (xylol, hematoxylin, alcohol, eosin), generated from immunostaining techniques.	160506	"Laboratory chemicals consisting of or containing dangerous substances, including mixtures of laboratory chemicals"

***Note: This classification is included as a general guideline of action, being under the final responsibility of the user the accomplishment of all the local, regional, and national regulations on the disposal of this type of materials.**

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16 LABEL AND BOX SYMBOLS

Explanation of the symbols of the product label and box:

IVD	In vitro diagnostic medical device		Expiration date
REF	Catalog number		Temperature limit
LOT	Lot code		Manufacturer
	Refer to the instructions for use		Sufficient content for <n> assays
	Safety data sheet		Distributor
	Importer		

17 CHANGE LOG

Date	Description
30/04/2024	Initial elaboration of the document.
03/03/2025	The document is updated to the new version of the template
08/09/2025	Section 7.9 is updated to include conditions in use of the product. Section 7.10 is updated to include the recommended buffer for the concentrated format. Section 9 is updated to include correct reference to Section 14 Section 14 is updated to include "Recommendations for the Safe Handling of Samples Suspected of Containing Prions"