DiaSource®

CE 0123 IVD

CT-U.S.-IRMA

REF **KIP0429**

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Instructions for Use

English

Please read this user manual carefully before use.

Other translations of this Instruction for Use can be downloaded from our website: https://www.DiaSource-diagnostics.com

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INSTRUCTIONS FOR USE (IFU) HISTORY

Version: 3.0

Date: 23.06.2026 - This version supersedes all earlier instruction manuals.

Content changes versus previous version:

Version number	Changes vs previous version
3	• A reference to the availability of translations in other languages has been added.
2	• The " Biological products from animal origin", "Human blood or plasma derived products" and "Irritant, sensitising, harmful" symbols were added in Section 14. • The warnings (Section 9) were updated. • The color square present on the components label was added in the Table of components in Section 4. • The Specimen stability was added in Section 6 and the Bibliography section was updated. • A table of the IFU history was added in replacement of the text.
1	• Restructured and rephrased for more clarity and alignment with requirements of "In Vitro Diagnostic Medical Devices Regulation" (IVDR) (EU) 2017/746. • In line with IVDR requirements, information/data have been added on sections Analytical Performance Characteristics, Clinical Performance Characteristics, Warnings and Precautions as well as Limitations. • The following sections were added: Important Notice and Symbols. • The Bibliography section was updated.

CT-U.S.-IRMA KIP0429

This device is an immunoradiometric assay (IRMA) (antibody-coated tube system) for the quantitative determination of human calcitonin in human serum.

FOR PROFESSIONAL USE ONLY

MAIN ASSAY FEATURES

Assay principle	immunoradiometric
Sample type	serum
Sample volume	200 µL
Incubation time	18 ± 1 hours at 2-8°C
Results are given in	pg/mL
Linear direct measuring range	8 - 700 pg/mL
Number of calibrators	6

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1. INTENDED PURPOSE

The DiaSource CT-U.S.-IRMA kit is a non-automated immunoradiometric assay (IRMA) intended to be used for the quantitative measurement of calcitonin (CT) in human serum by trained professionals in medical laboratories.
The *in vitro* diagnostic medical device is intended to be used for aiding to diagnosis, for monitoring and for post-operative follow-up of Medullary Thyroid Carcinoma (MTC).
The measurement of CT is useful in patients at risk of MTC due to hereditary traits or with thyroid nodular disease found by palpation or ultrasound, as well as in patients after thyroidectomy.

2. GENERAL INFORMATION

Medullary Thyroid Carcinoma (MTC) is a type of thyroid cancer affecting C cells and accounting for 15% of all thyroid cancer-related deaths (Thomas *et al*., 2019; Leimbach *et al*., 2021; Zarkesh *et al*., 2022). Interestingly, both healthy and neoplastic C cells secrete calcitonin, a 32-amino acid polypeptide hormone regulating calcium homeostasis, in the blood circulation (Pelizzo *et al.*, 2023; van Treijen *et al*., 2000; Kiriakopoulos *et al*., 2022).
Therefore, and because calcitonin level and tumor size are directly proportional (Zarkesh *et al.,* 2022), calcitonin is used for aiding MTC diagnostic. Calcitonin levels below 10 pg/mL are considered as a reliable sign of absence of any C cell disease (Verbeek *et al*., 2020; Garo *et al*., 2022; Leimbach *et al*., 2021; Li *et al.*, 2020), while MTC occurs in 50% of the cases at 70 pg/mL (Piticchio *et al*., 2023). Finally, metastatic diseases are suspected starting from 500 pg/mL (Kiriakopoulos *et al*., 2022; Leimbach *et al*., 2021; Li *et al*., 2020), which is close to the cut-off (466 pg/mL) at which MTC is suspected when performing stimulation tests (Fugazzola, 2023).
In addition, calcitonin (and particularly its doubling time) can also be used for monitoring and post-operative follow-up of MTC. A patient is considered as biochemically cured at post-operative levels below 10 pg/mL, while dissemination of a persistent or recurrent disease should be suspected from 150 pg/mL (Costante and Meringolo, 2020; Garo *et al*., 2022; Kiriakopoulos *et al*., 2022). On the other hand, a doubling time below 0.5 years is associated with a 5-year survival of 25%, while 100% of patients were alive at 10 years when the doubling time was over 2 years (Costante and Meringolo, 2020).
Serum calcitonin can be reliably measured using immunoassays, provided the use of “two-steps” assays maximizing the recognition of the mature monomer of calcitonin over the other isoforms, precursors, or degradation products.

3. TEST PRINCIPLE

The operation principle of immunoradiometric assays (IRMAs) is based on interactions of radio-labelled antibodies with epitopes on a target analyte. Such assays are used to detect very low concentrations of a target analyte.

A first antibody (i.e. the capture antibody) is attached to the surface of reaction tubes with the aim of capturing the target analyte and locating it to the reaction tubes. Then, the sample to be tested is added into the tubes where the target analyte (if present) binds to the capture antibody. In a next step, a detection (or labelled) antibody (labelled with a radioactive I-isotope, 125I), called tracer is added, and binds to the analyte as well (to a different epitope than the epitope recognized by the capture antibody). Following the immunologic reaction and formation of an immunocomplex, the tubes are finally washed to remove the excess unbound antibody. The gamma radiation emitted by the attached complexes is directly proportional to the concentration of analyte in the sample.

4. MATERIAL PROVIDED

The CT-U.S.-IRMA kit comprises the following major components:

Name	Symbol	Color code	Origin	Description	Reconstitution
Tracer (iodine 125 Ab)	Ab ^{125}I		BIO	1 vial (5.5 mL - 720 kBq) of Anti-CT-^{125}I (monoclonal antibody) in TRIS buffer with bovine serum albumin (BSA), azide (< 0.1%) and red dye.	Ready for use.
Coated tubes			BIO	2 x 48 tubes coated with anti-CT (monoclonal antibody).	Ready for use.
Calibrator 0	CAL 0			1 vial of lyophilized calibrator 0 in modified human plasma with gentamycin.	Add 1 mL distilled water.
DIL SPE	DIL SPE			1 vial of lyophilized specimen diluent (to be used for sample dilution) with gentamycin and thymol.	Add distilled water (see the volume on the label).
Control 1	CONTROL 1			1 vial of lyophilized Control 1 in human plasma with gentamycin (**see exact values on the label**).	Add 1 mL distilled water.
Control 2	CONTROL 2			1 vial of lyophilized Control 2 in human plasma with gentamycin (**see exact values on vial labels**).	Add 1 mL distilled water.
Calibrators 1-N	CAL N			5 vials of lyophilized calibrators (calibrators 1-5) in modified human plasma with gentamycin (**see exact values on vial labels**).	Add 1 mL distilled water.
WASH SOLN CONC	WASH SOLN CONC			1 vial of Wash Solution Concentrated (TRIS-HCl).	**Dilute** 70x with distilled water (use a magnetic stirrer).

5. MATERIAL NOT PROVIDED

The following material is required but not provided in the kit:

- Vortex mixer
- Magnetic stirrer
- 5 mL automatic syringe (Cornwall type) for washing
- Aspiration system
- Any gamma counter capable of measuring iodine-125 radiation may be used (with a minimal yield of 70%)
- Distilled water
- Pipettes for accurate delivery of different volumes (the use of accurate pipettes with disposable plastic tips is recommended)

6. SPECIMEN COLLECTION, HANDLING AND PREPARATION

Only the following specimen types must be used: human serum

It is the responsibility of the operator to ensure that the correct specimen types are used.

Observe the following recommendations for handling, processing and storing of samples:

- Specimen collection is performed according to Good Clinical Laboratory Practice (GCLP).
- The human blood collection is done by venipuncture in a serum separator or red top tube without anticoagulant.
- Human samples for calcitonin testing need to be transported to the laboratory on ice.
- The human serum should be promptly separated from blood cells, preferably in a refrigerated centrifuge.
- If samples are not assayed the same day as the blood collection, then it is advisable to freeze them until the assay.
- To enable samples to be retested, sample should be frozen in aliquots and discard each sample aliquot after first thawing (Soh & Aw, 2019; Perros *et al*., 2014).
- If a specimen is expected or known to have a concentration above the most concentrarted calibrator, it must be diluted with the specimen diluent so that its concentration falls within the measuring interval.

These human serum sample stabilities are given as an indication (Guder *et al.*, 2001):

Temperature	Time
Ambient (20 - 25°C)	4 hours
Refrigerated (2 - 8°C)	1 day
Frozen (preferred) (-20°C)	1 year

7. STORAGE CONDITIONS AND SHELF LIFE OF REAGENTS

Before opening or reconstitution, all kit components are stable until the expiration date indicated on the label if kept **at 2 to 8°C**, based on the assessment of the measurand drift following the guidelines of the CLSI document EP25-A.

After first use, the components are stable until the **kit expiration date** (indicated on the kit label), based on the assessment of the measurand drift following the guidelines of the CLSI document EP25, if stored and handled as indicated in the following **Table**:

Name	Storage temperature following first opening	Handling directions
Tracer (iodine 125 Ab)	2°C to 8°C	• Keep in the original, well-closed vial.
Coated tubes	NA	• Each tube can only be used once. • Remaining tubes must be stored at 2 to 8°C.
Calibrator 0	-15°C to -25°C	• Freeze immediately after use. • Only one freeze-thaw cycle allowed.
DIL SPE	-15°C to -25°C	• Freeze immediately after use. • Only one freeze-thaw cycle allowed.
Control 1	-15°C to -25°C	• Freeze immediately after use. • Only one freeze-thaw cycle allowed.
Control 2	-15°C to -25°C	• Freeze immediately after use. • Only one freeze-thaw cycle allowed.
Calibrators 1-N	-15°C to -25°C	• Freeze immediately after use. • Only one freeze-thaw cycle allowed.
WASH SOLN CONC	8°C to 25°C	• Prepare fresh. • Use on the same day.

8. TEST PROCEDURE

INTENDED USERS

The device shall be used only by trained professionals in medical laboratories equipped with radioactive safety procedures according to local regulations.

QUALITY CONSIDERATIONS

- Do not use the kit or components beyond expiry date.
- Do not mix components from different kit lots.
- Bring all the reagents to room temperature (18°C to 25°C) for 15 minutes prior to use.
- Thoroughly mix all reagents and samples by gentle agitation or swirling.
- In order to avoid cross-contamination, use a clean disposable pipette tip for the addition of each reagent and sample.
- High precision pipettes or automated pipetting equipment will improve assay precision.
- Respect the incubation times.
- Prepare a calibration curve for each run, do not use data from previous runs.
- Patient samples with a concentration above the measuring range are to be rated as "> most concentrated calibrator". The result must not be extrapolated. The patient sample in question should be diluted and retested.

- Patient samples with a concentration below the LoQ are to be rated as "< LoQ". The result must not be extrapolated.

REAGENTS PREPARATION

- **CT-US - IRMA - Tracer**:
  Ready for use.
- **CT-US - IRMA - Ab Coated Tubes**:
  Ready for use.
- **CT-US - IRMA - Calibrator 0**:
  Add 1 mL distilled water.
- **CT-US - IRMA - Diluent Spe.**:
  Add distilled water (see the volume on the label).
- **CT-US - IRMA - Control 1**:
  Add 1 mL distilled water.
- **CT-US - IRMA - Control 2**:
  Add 1 mL distilled water.
- **CT-US - IRMA - Calibrator 1-5**:
  Add 1 mL distilled water.
- **Commun - RIA/Elisa - Wash Solution - CE**:
  Dilute 70x with distilled water (use a magnetic stirrer).

PROCEDURE

1. Label coated tubes in duplicate for each calibrator, sample, and control. For the determination of total counts, label 2 uncoated tubes.

2. Homogenize calibrators, controls, and samples. Dispense 200 µL of each into the respective tubes.

3. Add 50 µL of anti-CT-^{125}I (tracer) to all tubes, including the uncoated tubes for total counts.

4. Shake the tube rack gently by hand to liberate any trapped bubbles.

5. Incubate for 18 ± 1 hours at 2-8°C.

6. Tubes for total counts are now set aside until the radioactivity is measured (step 8). Aspirate the content of the coated tubes (calibrators, controls and samples). Be sure to remove all the liquid since remaining droplets will increase the background counts per minute (cpm).

7. Wash the coated tubes twice with 2 mL of working wash solution and aspirate. Avoid foaming during the addition of the working wash solution. For manual washing procedure, first aspirate the foam layer and then the liquid. For automated wash cycles, continuous aspiration is recommended. The precision is improved by aspirating the tubes a second time two minutes after emptying the last tube.

8. Count all tubes, including the total count tubes, in a gamma counter for 60 seconds.

SUMMARY OF THE PROTOCOL

STEPS	TOTAL COUNTS (µL)	CALIBRATORS and CONTROLS (µL)	SAMPLES (µL)
Calibrators/Controls Samples Tracer	- - 50	200 - 50	- 200 50
Incubation	18±1 hours at 2-8°C		
Separation Washing solution Separation Washing solution Separation	- - - - -	Aspirate 2 mL Aspirate 2 mL Aspirate	
Couting	Count tubes for 60 seconds		

QUALITY CONTROL PROCEDURES

Good Clinical Laboratory Practices require that control samples are measured regularly to ensure the accuracy and precision of the assay. It is recommended to measure controls with each batch of measurements. These samples must be processed as indicated in the test procedure. It is recommended that the results are analyzed by using appropriate statistical methods. If the results obtained for controls are not within the range specified on the vial label, the results cannot be used unless a satisfactory explanation for the discrepancy has been given.

If desirable, each laboratory can make their own pools of control samples, which should be kept frozen in aliquots. Do not freeze-thaw more than once.

Acceptance criteria for the difference between the duplicate results of the samples should rely on Good Clinical Laboratory Practices.

CALCULATION OF RESULTS

1. Calculate the mean count rate of each sample (B) and relate it to the mean count rate of the total count (T). The results should be expressed as B/T (%).

2. Plot the mean percent value for each calibrator (ordinate) against the corresponding concentration (abscissa) and draw a calibration curve through the calibrator points. Reject the obvious outliers.

3. The mean percentage values B/T of the samples and controls are then used to determine the corresponding concentrations. Computer assisted data reduction will simplify these calculations. If automatic result processing is to be used, a 4 parameter logistic function curve fitting is recommended.

STANDARD CURVE EXAMPLE

The following data are for illustration only and should never be used instead of the real time calibration curve.

		cpm	B/T x 100 (%)
Total count		279092	100
Calibrators	0 pg/mL	164	0.06
	10 pg/mL	881	0.26
	31 pg/mL	1951	0.64
	49 pg/mL	3054	1.04
	157 pg/mL	8628	3.03
	686 pg/mL	39787	14.2

9. WARNINGS AND PRECAUTIONS

	Description
	Consult Instructions for Use (IFU).
	Do **not use after expiration date** specified on the label (format YYYY-MM-DD).
	Reagents from **different kit lots should not be mixed**.
	The concentration of the analyte in a given patient sample, determined with assays from **different manufacturers**, can **vary due to differences in assay methods, calibration, and reagent specificity**. **Values** measured with assays from different manufacturers **cannot be interchangeably used**.
	This kit **contains ^{125}I** (half-life: 60 days), emitting ionizing X (28 keV) and γ (35.5 keV) radiations. This **radioactive product** can be **transferred to and used only by authorized persons**; purchase, storage, use and exchange of radioactive products are **subject to the legislation** of the end user's country. In **no case** the product must be **administered to humans or animals**. All **radioactive handling** should be executed **in a designated area**, away from regular passage. A **logbook for receipt and storage** of radioactive materials must be kept in the laboratory. Laboratory **equipment** and glassware, which could be **contaminated** with radioactive substances, should be **segregated** to prevent cross contamination of different radioisotopes. Any **radioactive spills** must be **cleaned immediately** in accordance with the radiation safety procedures. The **radioactive waste** must be disposed of **following the local regulations and guidelines of the authorities** holding jurisdiction over the laboratory. Adherence to the basic rules of radiation safety provides adequate protection.
	This product contains concentrations of **azide** below the hazardous level which with repeated contact with lead and copper commonly found in plumbing drains may result in the build up of shock sensitive compounds. Sodium azide forms explosive compounds with heavy metals.
	The **human blood components** included in this kit have been tested by European approved and/or FDA approved methods and found **negative for HBsAg,**

	Description
	**anti-HCV, anti-HIV-1 and 2**. No known method can offer complete assurance that human blood derivatives will not transmit hepatitis, AIDS or other infections. Therefore, **handling of reagents, serum or plasma specimens should be in accordance with local safety procedures**.
	All **animal products and derivatives** have been collected **from healthy animals**. Bovine components originate from countries where bovine spongiform encephalopathy (BSE) has not been reported. Nevertheless, components containing animal substances **should be treated as potentially infectious.**
	Do **not smoke, drink, eat or apply cosmetics** in the working area.
	Observe the generally acknowledged safety precautions and laboratory techniques when handling reagents and patient samples.
	For more information, see **Material Safety Data Sheet (MSDS)**.

10. LIMITATIONS

- This product is **not** intended to be used as **a stand-alone diagnostic test**. The results of this test should only be interpreted in conjunction with other diagnostic measures, symptoms and clinical assessment.
- The **kit components** are stable until the expiry date if kept in indicated storage conditions and may be **reused only once**.
  Each **tube** can **only be used once**.
  Freshly prepared **working wash solution** should be **used on the same day**.
  Prepare a **calibration curve for each run**, do not use data from previous runs.
  Alterations in physical appearance of kit reagents may indicate instability or deterioration which may affect the performances. In this case, the kit reagents should **no longer be reused**.
- Specimens from patients who have received preparations of **mouse monoclonal antibodies for diagnosis or therapy** may contain **human anti-mouse antibodies (HAMA)**. Such specimens may show either **falsely elevated or depressed** values when tested with assay kits which employ mouse monoclonal antibodies.
- **Heterophilic antibodies** in human blood can react with reagent immunoglobulins, interfering with *in vitro* immunoassays.
  Patients routinely **exposed to animals or animal serum products** can be prone to this interference and **anomalous values may be observed in case of the presence of heterophilic antibodies**. Carefully evaluate the results of patients suspected of having these antibodies.
  If results are not consistent with other clinical observations, additional information should be required before diagnosis.
- Caution is advised when performing calcitonin determination in patients suffering of hyperbilirubinemia.

11. ANALYTICAL PERFORMANCE CHARACTERISTICS

Representative performance data are provided in this section. Assay results obtained in individual laboratories may vary from data presented.

ACCURACY OF MEASUREMENT

TRUENESS OF MEASUREMENT

The **%recovery** compared to the certified reference material is **comprised between 80 and 120%** for all samples tested.

Certified reference material	WHO International Standard NIBSC 89/620
Tested concentration range	12.5 - 1,000 pg/mL
Number of samples	21 (3 samples with 7 levels each)
Mean recovery (%)	96.6 %

PRECISION OF MEASUREMENT

Three human serum samples have been measured by **3 operators** on **5 days**, with **2 runs per day**, in **3 replicates** using **2 reagent lots**, according to the guidelines of the CLSI document EP05-A3. Results from this study for selected samples are summarized in the following **Table**:

Sample	Lot A				Lot B			
	Mean (pg/mL)	Repea-tability (%CV)	Within-laboratory (%CV)	Reprodu-cibility (%CV)	Mean (pg/mL)	Repea-tability (%CV)	Within-laboratory (%CV)	Reprodu-cibility (%CV)
1	**11.16**	16.8	19.6	22.2	**10.10**	9.6	13.6	13.6
2	**76.41**	5.7	8.2	8.4	**72.68**	7.9	9.4	9.4
3	**410.50**	5.8	7.2	7.2	**402.62**	4.3	8.9	8.9

ANALYTICAL SENSITIVITY

LIMIT OF BLANK (LoB)

The Limit of Blank (LoB) for the CT-U.S.-IRMA kit is 1.70 pg/mL, determined consistent with the guidelines of the CLSI document EP17-A2. **Four blank samples** (Cal0) have been measured by **1 operator** in **5 replicates** per run on **2 kit lots** for **3 days**.

LoB	1.70 pg/mL

LIMIT OF DETECTION (LoD)

The Limit of Detection (LoD) for the CT-U.S.-IRMA kit is 3.70 pg/mL, determined consistent with the guidelines of the CLSI document EP17-A2 and with proportions of false positives (α) less than 5% and false negatives (β) less than 5%; based on **240 determinations**, with **120 blank** and **120 low level replicates** (i.e. **4 blank samples** in **5 replicates** per run and **5 human serum samples** with low calcitonin level in **4 replicates** per run, measured by **1 operator** on **2 kit lots** for **3 days**); and an LoB of 1.70 pg/mL.

LoD	3.70 pg/mL

LIMIT OF QUANTITATION (LoQ)

The Limit of Quantitation (LoQ) for the CT-U.S.-IRMA kit is 7.86 pg/mL, determined consistent with the guidelines of the CLSI document EP17, based on **120 determinations** (i.e. **5 human serum samples** with low calcitonin level, measured by **1 operator** in **4 replicates** per run on **2 kit lots** for **3 days**) ; the LoQ was determined as the lowest calcitonin concentration that can be reproducibly measured with an **intermediate precision CV goal of 20%**.

LoQ	7.86 pg/mL

ANALYTICAL SPECIFICITY

INTERFERING SUBSTANCES

Potentially interfering substances were determined according to the guidelines of the CLSI documents EP07 and EP37. Substances tested for their potential to interfere with assay performance (see **Table**) were added to **2 different human serum samples** with calcitonin concentration between 17 and 419 pg/mL. They were found to **not interfere** (**allowable concentration difference** between samples with and without the interferent **< 15%**) **at the concentrations expected in the intended patient population** and **indicated** in the following **Table**:

Interfering substance	Tested concentrations
Bilirubin, conjugated	0.4 - 2.0 mg/dL
Calcium chloride	9 - 12 mg/dL
Glucose	40 - 220 mg/dL
Rheumatoid Factor	20 - 200 IU/mL
Total cholesterol	150 - 220 mg/dL
Triglycerides	100 - 250 mg/dL
Hemoglobin	250 - 500 mg/dL
Acetylsalicylic acid	20 - 40 mg/dL
Paracetamol	10 - 30 µg/mL
Prednisolone	3 - 30 µg/mL
Carbimazol	3 - 300 µg/mL
Dacarbazine	0.8 - 8 µg/mL
Doxorubicin	640 - 1,920 ng/mL
Propylthiouracyl	5 - 10 µg/mL
Vandetanib	500 - 1,000 ng/mL

For unconjugated bilirubin, an interference was observed at 15 mg/dL only in case of sample 1 (around 50 pg/mL). However, the typical reference values for unconjugated bilirubin in human is 0.2 - 0.8 mg/dL and no interference was observed at 2 mg/dL. Consequently, we advise **caution** when performing calcitonin determination **in patients suffering of hyperbilirubinemia**.

CROSS-REACTIVE SUBSTANCES

Potentially cross-reactive substances (i.e. interferents structurally similar to the antigen of interest) were tested according to the guidelines of the CLSI document EP07. Substances assayed for their potential to interfere with assay performance (see **Table**) were added to **2 different human serum**

samples with calcitonin concentration between 46 and 346 pg/mL. They were found to **not cross-react** (**allowable concentration difference** between samples with and without the cross-reactive substance, **relative to the concentration of the cross-reactive substance < 15%**) **at the concentrations indicated** in the following **Table**:

Interfering substance	Tested concentrations
Salmon calcitonin	0.01 - 0.10 - 1 µg/mL
α-CGRP	0.01 - 0.10 - 1 µg/mL
Calcitonin-carboxypeptide I (CCP-I)	0.01 - 0.10 - 1 µg/mL
Aminoprocalcitonin	0.01 - 0.10 - 1 µg/mL
Procalcitonin	0.01 - 0.10 - 1 µg/mL

METROLOGICAL TRACEABILITY OF CALIBRATOR AND CONTROL MATERIAL VALUES

The CT-U.S.-IRMA kit is calibrated against the Calcitonin (human) WHO International Standard NIBSC 89/620. This calibration is verified on a regular basis by regression analysis and comparison to theoretically expected results using 1 reagent lot.

The calcitonin measurement results are given in pg/mL.

The uncertainty of assigned values for the CT-U.S.-IRMA kit calibrators is %ru(y) = 18.36%.

MEASURING RANGE OF THE ASSAY

LINEARITY

The kit was tested for linearity from **8 to 700 pg/mL** and has been demonstrated to **be linear** with a **maximum allowable nonlinearity of 10%**, according to the guidelines of the CLSI document EP06.

HIGH DOSE HOOK EFFECT

According to the guidelines of the CLSI document EP34, no high dose hook effect can be observed **up to 1,000,000 pg/mL**, which is beyond the highest possible concentration found in clinical practice.

DEFINITION OF ASSAY CUT-OFF

The assay cut-off was determined according to literature search to be 13.69 pg/mL (Meghelli *et al.*, 2018).

12. CLINICAL PERFORMANCE CHARACTERISTICS

REFERENCE RANGE

A reference range was established based on **human serum samples from 192 presumed healthy individuals**.
The characteristics of the reference interval is given in the following **Table**:

Identification	N	Mean (pg/mL)	Median (pg/mL)	SD (pg/mL)	95% upper reference limit (pg/mL)	90% CI (pg/mL)
Presumed healthy individuals	192	4.58	3.90	2.70	10.93	8.90 - 12.26

Representative performance data are provided in this section. Results obtained in individual laboratories may vary.

INTERPRETATION OF RESULTS

Analyte values need to be evaluated in combination with clinical symptoms and/or other laboratory parameters. Values higher than the 95% upper reference limit, as stated in the Table above, should be considered pathological with respect to the intended use and under consideration of the limitations.

Note: It is recommended that each laboratory establishes its own reference range based on representative patient collectives and/or test the validity of the manufacturer's commercial test kit data.

DIAGNOSTIC SPECIFICITY AND SENSITIVITY

Several studies support the use of CT testing with the CT-U.S.-IRMA kit for aiding MTC diagnosis. Indeed, the study of Meghelli *et al*. (Meghelli *et al.*, 2018) states clinical performance of high quality, notably a high specificity (98%) and sensitivity (83%). The advantage of using CT measurements (and particularly with the CT-U.S.-IRMA kit) over other diagnostic techniques for MTC was confirmed by Hahm *et al*. (Hahm *et al.*, 2001). They calculated cut-off values consistent with the literature for other CT-measuring devices (Hahm *et al.*, 2001). Finally, Vardarli *et al.* (Vardarli *et al.*, 2021) show high clinical performance indicators, such as the sensitivity (0.99), specificity (0.99), positive likelihood ratio (72.4) and negative likelihood ratio (0.01).

The second clinical benefit intended by the CT-U.S.-IRMA kit, i.e. the post-operative follow-up of MTC, is also proved in the literature. Particularly, Barbet *et al*. (Barbet *et al.*, 2005) show that the CT-U.S.-IRMA kit is able to produce cut-off doubling times in line with those presented in the literature for other devices, thereby proving the clinical relevance of both the CT doubling time and the CT-U.S.-IRMA kit. The same stands for the work of Cho *et al*. (Cho *et al.*, 2016) and Jung *et al*. (Jung *et al.*, 2016) about the post-operative thresholds for structural recurrence and biochemical remission.

13. IMPORTANT NOTICE

Any serious incident that has occured in relation to the device shall be reported to DIAsource ImmunoAssays S.A. and to the Competent Authority of the country in which the user and/or the patient is established.

The Summary of Safety and Performance is available upon request.

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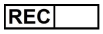
15. SYMBOLS

Symbols used in Instructions for Use and Product Labelling of DiaSource CT-U.S.-IRMA kit are summarized in the following Table, except for symbols of the kits components that are present in the section "4. MATERIAL PROVIDED":

Symbol	Title	Description
	Manufacturer	Indicates the manufacturer of the medical device. This symbol is accompanied by the name and address of the manufacturer adjacent to the symbol.
	Date of manufacture	Indicates the date on which the medical device was manufactured. The date is expressed in the form YYYY-MM-DD.
	Use-by date	Indicates the date after which the medical device must no longer be used. The date is expressed in the form YYYY-MM-DD.
	Lot Number	Indicates the manufacturer's batch number.
	Catalog number	Indicates the manufacturer's catalog number.
	Temperature limit	Indicates the minimum and maximum temperatures to which the medical device can be safely exposed, e.g. 2°C to 8°C.
	Biological risks	Indicates that there are potential biohazards associated with the medical device.
	Do not re-use	Indicates a component or kit intended for single-use.
	Consult Instructions for Use	Indicates that it is necessary to consult the Instructions for Use.
	*In vitro* diagnostic medical device	Indicates a medical device that is intended to be used as an *in vitro* diagnostic medical device.
	Contains sufficient for	Indicates the total number of tests that can be performed with the medical device, e.g. 96.
	Not for self-testing	Indicates that the product cannot be used by a patient himself but must be used in a laboratory.
	Translation	Indicates that the original information of the medical device has been translated in addition to or instead of the original information.
	CE Marking	CE Conformity Marking according to Regulation (EU) 2017/746 on *In Vitro* Diagnostics Medical Devices, with registration number of Notified Body.
	Unique Device Identification	Indicates a carrier which contains information about a unique device identification.
	Human blood or plasma derived products	Indicates an in vitro diagnostic medical device that contains or incorporates products derived from human blood or plasma.

Symbol	Title	Description
	Biological products from animal origin	Indicates an in vitro diagnostic medical device that contains biological tissues or cells, or derived elements from animal origin.
	Lyophilized product	Indicates that the product is lyophilized.
	Reconstitution	Indicates that the product must be reconstituted in the volume indicated in the box on the right.
	Radioactive	Indicates the presence of a radioactive substance.
	Irritant, sensitising, harmful	These are substances which, absorbed through the skin, may give rise to such a reaction of hypersensitisation (hypersensitivity) that subsequent exposure to the substance or preparation will cause characteristic adverse effects.