REF 47745 ZENIT ra autoimmunity	**ZENIT RA Anti-TG**	Distributed by A.MENARINI diagnostics
INSTRUCTIONS FOR USE EN *English*	IVD +2°C +8°C Σ 100	CE

USAGE

The *ZENIT RA Anti-TG (Anticorpi Anti tireoglobulina)* test is a chemiluminescent immunoassay (CLIA) used for quantitative determination, using *ZENIT RA Analyser o IDS-iSYS Multi-Discipline Automated System* instrumentation, of specific IgG class antibodies acting against human thyroglobulin, in samples of human serum or plasma (EDTA, Eparina or Sodium Citrate).
This dosage is used as a diagnostic aid when assessing autoimmune thyroid diseases.
This product must be used in strict compliance with the instructions given in this document by professional users.

CAUTION: Medical decisions must not be based exclusively on the result of this test, but must take into account all available clinical and laboratory data as a whole.

CLINICAL SIGNIFICANCE

The autoimmune thyroid diseases (TA) are the most frequent among all autoimmune diseases. In the blood of patients with thyroid disease it is possible to isolate abnormal antibodies, which create self-toxicity phenomena attacking the gland and compromising its correct functionality. The dosage of these antibodies is useful to recognize the basis of autoimmune thyroid disease and to distinguish them from other forms that do not affect the immune system [1,2].
The anti-thyroid antibodies used in clinical practice are those acting in particular against thyroglobulin (anti-TG) and thyroid peroxidase (anti-TPO, initially known as microsomal antibodies).
High levels of these antibodies are recorded both in chronic *Hashimoto*[3] thyroiditis that in *Graves-Basedow's* disease; the distinction between the two diseases is however easy since the first is typically associated with hypothyroidism, while the *Graves-Basedow's* disease typically correlates with hyperthyroidism.
The thyroglobulin [4] is a glycoprotein molecule, precursor of thyroid hormones (thyroxine T4 and triiodothyronine: T3), synthesized through the iodine organification in its tyrosine residues by the thyroid peroxidase enzyme.
Anti-TG autoantibodies are present in the majority of patients with chronic *Hashimoto's* thyroiditis or postpartum thyroiditis. There are present also in 30% of patients with *Graves-Basedow* disease. The test can be positive even in patients with thyroid cancer or other forms of thyrotoxicosis, and in carriers of non-thyroid

autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, diabetes mellitus type 1, atrophic gastritis and Addison's disease. Also pregnancy may be associated to the appearance of anti-thyroglobulin antibodies in the blood.

Thyroid peroxidase (TPO) [5] is an enzyme concentrated in the thyroid follicular cells, essential for the synthesis of thyroid hormones T4 and T3 from thyroglobulin. Anti-TPO autoantibodies are found in the serum of almost all patients with chronic *Hashimoto's* thyroiditis and in about half of people with *Graves-Basedow* disease. Similar to what was considered for the anti-thyroglobulin autoantibodies, high antibody titres are also present in patients with organ-specific non-thyroid diseases and in about 10% of normal individuals. A similar situation occurs during pregnancy, for which there is an increased risk of developing postpartum thyroiditis in case anti-thyroid peroxidase positivity in the first quarter. Also peculiar of *Graves-Basedow* disease are anti-thyroid antibodies acting against the TSH[6] receptor, the pituitary hormone that stimulates the gland to synthesize thyroid hormones; it is the stimulation of these receptors induced by antibodies that enhance the synthesis of T3 and T4, configuring the typical context of hyperthyroidism often associated with goiter.

Slightly or moderately elevated levels of anti-thyroid antibodies can also be observed in healthy patients, with a normal thyroid function; these individuals must still be monitored over time, since an increased risk of future thyroid disease related to the presence of these antibodies is determined [7,8].

PRINCIPLE OF THE METHOD

The *ZENIT RA Anti-TG* kit for quantitative determination of specific IgG class antibodies acting against human thyroglobulin employs an indirect two-step immunological method based on the principle of chemiluminescence.

The specific antigen used to coat the magnetic particles (solid phase) and an anti-human IgG antibody are marked with an acridinium ester derivative (conjugate).

During initial incubation, the specific antibodies present in the sample, in the calibrators or in the controls bond with the solid phase.

During the second incubation, the conjugate reacts with the Anti-TG antibodies sequestered by the solid phase.

After each incubation, the material that has not bonded with the solid phase is removed by aspiration and subsequent washing.

The quantity of marked conjugate that remains bonded to the solid phase is assessed by activation of the chemiluminescence reaction and measurement of the luminous signal. The generated signal, expressed in relative light units (RLU), is indicative of the concentration of specific antibodies present in the sample, in the calibrators and in the controls.

AUTOMATION

The *ZENIT RA Analyser* automatically performs all the operations envisaged by the dosage protocol: addition of samples, calibrators, controls, magnetic particles, conjugates and chemiluminescence activation solutions to the reaction container; magnetic separation and washing of particles; measurement of the light emitted.
The system calculates the dosage results for the samples and controls by means of a stored calibration curve and prints a report that includes all the information related to the dosage and to the patient.

MATERIALS AND REAGENTS

Materials and reagents supplied

REAG	1	MP	2.5 mL

Magnetic particles coated with native thyroglobulin antigen in TRIS Buffer containing stabilising proteins, surfactant, Pro-Clin 300 and sodium azide (< 0.1 %) as preservatives.

REAG	2	CONJ	25 mL

Monoclonal rat anti-IgG antibody marked with an acrinidium ester derivative (conjugate), in Phosphate Buffer containing stabilisers, surfactant, Pro-Clin 300 and sodium azide (< 0.1 %) as preservative.

REAG	3	DIL	25 mL

Sample Diluent Solution: Phosphate Buffer containing bovine serum albumin, a surfactant, an inert blue colouring agent, Pro-Clin 300 and Gentamicin SO4 as preservatives.

REAG	4	CAL A	1.6 mL

Serum with low concentration of Anti-TG antibodies in Phosphate Buffer containing bovine serum albumin, a surfactant, an inert blue colouring agent, Pro-Clin 300 and Gentamicin SO4 as preservatives.

REAG	5	CAL B	1.6 mL

Serum with high concentration of Anti-TG antibodies in Phosphate Buffer containing bovine serum albumin, a surfactant, an inert blue colouring agent, Pro-Clin 300 and Gentamicin SO4 as preservatives.

All reagents are ready for use.
Reagents 1, 2 and 3 are assembled in a single kit forming the reagent cartridge.
The Calibrator concentrations are expressed in IU/mL (International Units) and calibrated against WHO International Reference Preparation Anti-thyroglobulin 1st IRP 65/093. The concentration settings, specific for each production batch, are recorded on the DATA DISK included in the kit.

DATA DISK

A Mini-CD containing data regarding all the products in the ZENIT RA line (Reagents, Calibrators, Control Serums) updated to the last production batch with the exclusion of products that have expired at the date when the new DATA DISK was compiled.
Only the DATA DISK with the highest batch number needs to be kept to maintain the information required for correct operation of the system up to date.

Materials and reagents required but not supplied in the kit:

- ZENIT RA Analyzer [1] — Cod. No. 41400
- ZENIT RA Cuvette Cube[1] — Code No. 41402
  Pack of 960 cuvettes
- ZENIT RA System Liquid [2] — Code No. 41409
  1 bottle containing 5 litres of ready-to-use solution
- ZENIT RA Wash Solution [2] — Code No. 41407
  1 bottle containing 10 litres of ready-to-use solution
- ZENIT RA Trigger Set ([2] — Cod. No. 41403
  1 250 mL-bottle of Trigger A (pre-trigger solution)
  1 250 mL-bottle of Trigger B (trigger solution)
- ZENIT RA D-SORB Solution — Cod. No. 41436
  Pack of 2 bottles containing 1 litre of ready-to-use solution
- ZENIT RA Cartridge Checking System[2] — Cod. No. 41401
- ZENIT RA Top Cap Set — Code No. 41566
  300 red top caps to close the calibrator containers after first use.

[1] Made by IDS France SAS, 42 rue Stéphane Mazeau, 21320 Pouilly en Auxois, France and distributed by A. Menarini Diagnostics Srl.
[2] Made by IDS SA, 101-103 rue Ernest Solvay, 4000 Liège, BELGIUM and distributed by A. Menarini Diagnostics Srl.

Other Recommended Reagents

ZENIT RA THYROID CONTROL SET Code No. 47760

Three 1.5 mL vials of negative human serum and three 1.5 mL vials of human serum positive for anti-TG antibodies.

WARNINGS AND PRECAUTIONS

The reagents supplied in the *ZENIT RA Anti-TG* kit are only for in vitro diagnostic use and not for in vivo use in humans or animals.

This product must be used in strict compliance with the instructions given in this document by professional users.

Menarini cannot be held responsible for any losses or damages caused by use not in conformity with the instructions supplied.

Safety precautions

This product contains material of animal origin and therefore must be handled as if it contains infecting agents.

This product contains components of human origin. All units of serum or plasma used to produce the reagents in this kit have been analysed with FDA-approved methods and found not to be reactive due to presence of HBsAg, anti-HCV, anti-HIV1 and anti-HIV2.

However, since no analysis method is able to guarantee the absence of pathogenic agents, all material of human origin must be considered to be potentially infected and handled as such.

In the event of damaged packaging or accidental leakage, decontaminate the area concerned with a diluted solution of sodium hypochlorite after putting on suitable personal protective equipment (overall, gloves, goggles).

Dispose of the material use for the clean-up and of the packaging involved in the leakage according to national regulations for disposal of potentially infected waste.

In case of damaged packaging with leaking liquid, reagents must not be used for the execution of the dosages.

Some reagents contain sodium azide as a preservative. Since sodium azide may react with lead, copper and leaded brass forming explosive azides in piping, it is recommended that reagents or waste are not poured down drains but are disposed of in compliance with the national regulations on disposal of potentially hazardous waste.

Operating precautions

Reliable results can only be obtained by strictly complying with these instructions and scrupulously following what is written in the operating manual for the instrument.

The reagents supplied in the kit must be used only with the *ZENIT RA Analyser* system.
The components of the reagent cartridge must not be removed from the cartridge and reassembled.
Do not use the kit after its use-by date.

PREPARATION OF THE REAGENTS

The reagents supplied in the kit are all ready for use.

PRESERVATION AND STABILITY OF THE REAGENTS

Store the reagents supplied in the kit at 2-8°C in a vertical position in a dark place.
In these conditions unopened reagent cartridge and calibrators are stable up to the use-by date.
After opening the reagent cartridge can be used for 60 days if kept in a refrigerator at 2-8°C or in the analyser.
After opening, the calibrators can be used for 60 days if kept in a refrigerator at 2-8°C and if they have not been left in the analyser for more than 6 hours per session.
Do not freeze the reagents and calibrators.

PREPARATION AND PRESERVATION OF SAMPLES

Dosage must be performed on samples of human serum and plasma (EDTA, Eparina or Sodium Citrate).
Use of lipaemic, haemolysed and turbid samples is not recommended.
Separate the serum from the clot or the plasma from the red globules, transferring them from the primary separating tubes with gel in secondary tubes with no additives, as soon as possible.
Before being analysed, samples may be kept in a refrigerator at 2-8°C for a maximum of 7 days.
If the dosage is to be performed after more than 7 days, store the samples frozen (< - 20°C).
Avoid repeated freezing and thawing.

OPERATING PROCEDURE

Scrupulously follow the instructions given in the operating manual of the instrument to obtain reliable analytical results.

Loading of reagents
All the reagents supplied in the kit are all ready for use.
Before inserting the reagent cartridge in the system, the magnetic particle container must be horizontally agitated by rotation in order to favour resuspension of the particles. Avoid generating foam when performing this operation.
Place the reagent cartridge in the reagent area of the instrument using the guide provided and leave it to be agitated for at least 40 minutes before use.

Positioning of the reagent cartridge simultaneously determines reading of the identity bar-code. If the cartridge label is damaged or if it is not readable, the reagent cartridge identification data can be entered manually.
The instrument automatically maintains the magnetic particles constantly agitated.
If the reagent cartridge is removed from the instrument, store it at 2-8°C in a vertical position in a dark place.

Loading of calibrators

ZENIT RA calibrators are ready for use. Leave the calibrators at room temperature for 10 minutes and then gently shake the contents, either manually or using a vortex, avoiding the formation of foam.
When using the calibrators for the first time, remove the guarantee seal and the white sealing cap before placing them in the analyser.
If the calibrators have already been used, the container will have a top cap (red cap) with no guarantee seal. Remove the red closing cap before placing them in the analyser.
Place the calibrators in the samples area of the analyser; see the analyser user manual on how to identify them in the analyser. Bar-code data must be entered manually if the label is damaged or if it is unreadable.
The readings for the anti-TG antibody concentration in the calibrators are recorded in the DATA DISK and automatically transferred to the analyser.
At the end of the session, the calibrator containers must be closed with the top caps (red caps) provided and stored at 2-8°C until they are used again.
The calibrators can be used for a maximum of four times.

Loading of controls

Place the controls in the samples area of the analyser. See the analyser user manual on how to identify them in the analyser. If there is no bar-code on the control or if it is not readable, the control identification data must be entered manually. If ZENIT RA Controls are used, see the usage instructions provided. The readings for the anti-TG antibody concentration in the ZENIT RA controls are recorded in the DATA DISK and automatically transferred to the analyser.
Select the required parameters for each control.

Loading of samples

Place the samples in the samples area of the analyser; see the analyser user manual on how to identify them in the analyser. If there is no bar-code on the sample or if it is not readable, the sample identification data must be entered manually.
Select the required parameters for each sample.

Calibration

The *ZENIT RA Analyser* instrument uses a memorised calibration curve (master curve), generated by the manufacturer for each batch of reagent cartridges.
The “master curve” parameters, together with the calibrator concentration settings, are stored in the DATA DISK and transferred to the instrument’s data base.
Calibrators A and B are used to recalibrate the “master curve” in both for the instrument used and for the reagents on board.

To perform recalibration analyse the two calibrators A and B in triplicate and the controls singly. The concentration readings obtained with the controls make it possible to validate the new calibration.
Once recalibration of the “master curve” has been accepted and memorised, all subsequent samples can be analysed without any further calibration, except in the following cases:

- when a reagent cartridge with a new batch number is loaded into the instrument;
- when the control readings do not fall within the range of acceptability;
- when the instrument maintenance procedure is performed;
- when the validity of the recalibrated “master curve” has expired.

The validity of the recalibrated “master curve” for the *ZENIT RA Anti-TG* kit is 21 days.
Control of recalibration is performed automatically by the instrument.

Dosage

Press the start button.

1. The system aspirates 100µL of Sample Diluent, 20µL of Magnetic Particles, 100µL of Sample Diluent and 6µL of the sample or control (for the calibrators, the positive serum is supplied prediluted with the Sample Diluent and the volume taken is 106µL). The aspirated solutions and suspension are dispensed into the reaction cuvette.
2. The reaction cuvette is incubated in the rotor at 37°C for 10 minutes.
3. After this phase of incubation, the magnetic particles are separated and washed.
4. 200 µL of conjugate are dispensed into the cuvette.
5. The reaction cuvette is incubated in the rotor at 37°C for 10 minutes.
6. After this last phase of incubation, the magnetic particles are separated and washed and the cuvette is transferred to the reading chamber.
7. The quantity of conjugate bonded to the solid phase, expressed in RLU, is directly proportionate the concentration of anti-TG antibodies present in the sample.
8. The responses obtained are interpolated on the calibration curve and transformed into concentrations.

QUALITY CONTROL

To ensure the validity of the dosage, control serums at differing levels of concentration (at least one negative serum and one positive serum) must be measured every day in which dosage is performed.
If your laboratory requires a more frequent use or a higher number of controls to check the dosage results, comply with the set quality control procedure.
If ZENIT RA control serums are used, the expected average readings and the acceptability limits are those given on the DATA DISK included in the control pack too.
If different control serums are used, before using them, the readings expected with ZENIT RA reagents and system must be defined.
If the control reading does not fall within the specified range of acceptability, the related dosage results are not valid and the respective samples must be analysed again.
In this case, before repeating the dosage, a recalibration procedure must be performed.

CALCULATION AND INTERPRETATION OF THE RESULTS

Calculation of the results

The concentration of the anti-thyroglobulin antibodies present in the samples that are being tested is automatically calculated by the system. The readings can be viewed on the display or printed.

The concentrations are expressed in IU/mL.

Calculation of the analyte concentration in the sample takes place by reading the response obtained for each sample on a calibration curve processed by a logistic “fitting” system with four parameters (4PL, Y weighted), periodically corrected according to the responses obtained for dosage of the calibrators.

For detailed information on how the system calculates the results, please see the operating manual for the system.

Interpretation of the results

The measurable range for the *ZENIT RA Anti-TG* dosage is: 0.0 – 5500 IU/mL.

Readings lower than 0.0 IU/mL are extrapolated values, the message “OMR-” and/or ORA appears and they are shown as “equal to 0.0 IU/mL”.

Readings higher than 5500 IU/mL are accompanied by the message “OMR+” and/or ORA and may be retested after suitable dilution.

The results of the samples may be interpreted in the following way:

(IU/mL)	Interpretation
< 50 antibodies	The sample must be considered to be negative for the presence of anti-thyroglobulin
50 ÷ 75 antibodies	The sample must be considered to be uncertain for the presence of anti-thyroglobulin
> 75 antibodies	The sample must be considered to be positive for the presence of anti-thyroglobulin

The above readings are to be considered only suggested readings. Each laboratory must establish its own reference ranges.

DOSAGE LIMITS

For diagnostic purposes, the results obtained with the *ZENIT RA Anti-TG* kit and the *ZENIT RA Analyser* system must be used together with the other clinical and laboratory data available to the physician.

Bacterial contamination of the sample and heat inactivation may influence the result of the dosage.

Heterophyllous antibodies present in human serum samples may react with immunoglobulin-based reagents, causing interference with in vitro immunological dosages. Such samples may give rise to anomalous readings if analysed with the *ZENIT RA Anti-TG* kit.

EXPECTED READINGS

The samples of 133 individuals selected randomly from the normal routine work of the laboratory were analysed to check the presence of anti-thyroglobulin antibodies.
All samples analysed proved negative, with an average reading of 3.5 IU/mL and a standard deviation of 5.62 IU/mL.
Using the results obtained the “Limit of Blank” (LoB = the highest reading that can be expected in a series of samples that do not contain the analyte) was calculated. The “Limit of Blank”, determined as 95° perce ntile of the negative population, proved equal to 5.2 IU/mL with the Reagent batch no. 3.

DIAGNOSTIC SENSITIVITY AND SPECIFICITY (CLINICAL)

A total of 70 samples were tested with the ZENIT RA Anti-TG, of which 16 samples from patients with Hashimoto’s thyroiditis, 4 samples from patients with Graves’ disease, 50 samples presumably normal, from the laboratory routine.

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- **Diagnostic specificity: 96 % (48/50)**
  Of the 50 samples from patients presumably normal, from the laboratory routine 48 were negative, 1 uncertain and 1 positive.

- **Diagnostic sensitivity: 70 % (14/20)**
  Of the 16 samples from patients with Hashimoto’s thyroiditis 11 were positive, 2 uncertain and 3 negative.
  Of the 16 samples from patients with Graves’ disease 3 were positive and 1 negative.

Based on the diagnostic specificity and sensitivity results, **the diagnostic agreement is 88.6 % (62/70).**

PERFORMANCE

Warning: the data presented do not represent the operating specifications of the kit, but serve as experimental proof of how the kit works within these specifications in the manner envisaged by the manufacturer.

Precision and Reproducibility

The precision and the reproducibility of the *ZENIT RA Anti-TG* kit have been assessed using a protocol based on the guidelines given in Clinical and Laboratory Standards (CLSI) document EP5-A2.

The ***precision*** was calculated by analysing the results of 20 replicates of four serums (one negative and three positive with differing concentrations of thyroglobulin antibodies) performed with two different batches of reagents in the same test session.

The concentration of the negative anti-thyroglobulin serum (N1) was always 0.0 IU/mL with reagent batches nos. 1 and 2.

The table shows the results obtained with the 3 positive serums.

Sample	Reagents Batch no.	Average Concentration average (IU/mL)	SD	CV %
1	1	275.4	16.05	5.8
	3	299.4	17.23	5.8
2	1	1364.5	27.61	2.0
	3	1305.4	32.89	2.5
3	1	2120.5	36.25	1.7
	3	2104.8	44.13	2.1

The ***reproducibility*** was calculated by analysing the results of the determination of six serums (one negative and five positive with differing concentrations of anti-thyroglobulin) performed singly, in 45 different sessions, with two different batches of reagents.

The concentration of the negative anti-thyroglobulin serum (N1) was always within the range from 0.2 and 10.7 IU/mL.

The table shows the results obtained with the 5 positive serums.

Sample	Average Concentration average (IU/mL)	SD	CV %
1	217.0	10.38	4.8
2	292.7	17.70	6.0
3	388.6	20.86	5.4
4	958.6	81.89	8.5
5	1903.3	155.18	8.2

Analytical Sensitivity

The analytical sensitivity of the *ZENIT RA Anti-TG* kit was assessed using a protocol based on the guidelines given in Clinical and Laboratory Standards (CLSI) document EP17-A.

In one case referred to as the ***Limit of Detection*** *(LoD:* that is the smallest quantity of analyte that the method is able to measure*)* the formula for calculating LoD = LoB + C_β SD_s (in which LoB is the "Limit of Blank", SD_s is the estimated standard deviation of the distribution of the sample at low concentration and C_β is derived from 95 °percentile of the standard Gau ssian distribution) was applied.

Four low concentration samples of analyte were used, determined singly with three batches of reagents in 15 different tests.

The Limit of Detection of the *ZENIT RA Anti-TG kit* proved to be 16.5 IU/mL.

In the other protocol, calculation of the **Minimum Detectable Concentration** (MDC) is envisaged: 20 replicates of the solution of the 0 AU/mL Standard of the Master curve were used. The average and the standard deviation (DS) were formulation on a batch of the kit. The RLU value related to the average + 2.6 DS was interpolated on the curve and the related concentration was obtained from this value.

The analytical sensitivity expressed as the Minimum Detectable Concentration is 0.6 IU/mL.

The minimum detection values, together with considerations of a clinical kind and the results of comparison with reference methods contributed to the definition of the cut-off value.

Analytical Specificity: Interferences

A study based on the guidelines given in the CLSI document EP7-A2 has shown that the dosage performances are not influenced by the presence in the sample of the potentially interfering substances listed in the table below, up to the tested concentration.

Potentially Interfering Substances	Maximum tested concentration
Free bilirubin	20 mg/dL
Conjugated bilirubin	20 mg/dL
Haemoglobin	1000 mg/dL
Triglycerides	3000 mg/dL

Use of lipaemic, haemolysed and turbid samples is not in any case recommended.

Analytical Specificity: Cross reactions

In order to assess potential cross reactions of the antigen used to sensitise the microparticles, a study was conducted using 32 samples, all with high levels of other antibodies and negative for anti-thyroglobulin IgG.

The samples used were subdivided as follows: SS-A (2), SS-B (2), U1-snRNP (2), Jo-1 (2), Scl-70 (2), Cenp B (2), Sm (2), PR3 (2), MPO (2), β_2-GLI/CL (2), Gliadin (2), t-TG (2), CCP (2), GBM (2), dsDNA (2) and Rheumatoid Factor (RF) (2).

The study did not show any significant cross reaction to the antigen in the solid phase with the other antibodies.

Saturation effect at high doses

Some immunological methods used to determine samples containing the analyte at extremely high concentrations may supply apparent levels of underestimated analyte (Hook effect).

The method used in the *ZENIT RA Anti-TG* kit, since it uses two incubations, is not subject to this effect.

A sample with an extremely high concentration (above the measurement range) of anti-thyroglobulin antibodies confirmed the absence of the “hook” effect up to the concentration of 53854 IU/mL.

Relative Sensitivity and Specificity

The presence of anti thyroglobulin antibodies was determined using the ZENIT RA *Anti-TG* kit and an ELISA dosage method available on the market in 250 samples:
9 samples gave rise to discordant results between the ZENIT RA dosage and the ELISA dosage available on the market.
The ***relative concordance*** was therefore found to be 96.4 % (95% Confidence Interval: 93.0–98.2 %) (241/250)
The ***relative sensitivity*** was therefore found to be 94.1 % (95% Confidence Interval: 82.8–98.5%) (48/51).
The ***relative specificity*** was therefore found to be 97.0 % (95% Confidence Interval: 93.2– 98.8%) (193/199).

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