Snibe Diagnostic

CE REF 130270002M:100 tests/kit
130670002M: 50 tests/kit
130770002M: 30 tests/kit

MAGLUMI® Cortisol (CLIA)

INTENDED USE

The kit is an *in vitro* chemiluminescence immunoassay for the quantitative determination of Cortisol in human serum, plasma and urine using the MAGLUMI series Fully-auto chemiluminescence immunoassay analyzer and Biolumi series Integrated System, and the assay is used for an aid in the diagnosis and treatment of disorders of individuals with suspected or confirmed the adrenal gland.

SUMMARY

Cortisol is a glucocorticoid hormone secreted by the outer cortex of the adrenal gland and it is an important adrenal biomarker[1,2]. CRH (corticotrophin releasing hormone) and ACTH (adrenocorticotrophic hormone) stimulate cortisol secretion through a feedback control[1]. The HPA is the primary endocrine stress axis in man. Secretion of cortisol from the adrenal cortex is regulated by a complex system of long and short feedback loops[3].

Cortisol can be measured in serum, urine or saliva. The major fraction of cortisol circulates bound to the plasma protein corticosteroid binding globulin (CBG or transcortin) and to albumin, these prevent the hormone penetrating the membrane of the target cells. Only 3–5% of the total plasma cortisol circulates in the unbound free cortisol form, namely the bioactive form[1].

Cortisol levels in the body fluids are characterized by circadian rhythm with a morning maximum, declining levels throughout the daytime, a period of low concentration around midnight and a rise after the first few hours of sleep[1].

Over-or underproduction of cortisol can result in the devastating diseases of Cushing's and Addison's respectively[4]. Cortisol withdrawal increased insulin sensitivity in terms of increased glucose oxidation and decreased endogenous glucose production; this may induce hypoglycemia in adrenocortical failure[5]. Hypopituitarism is associated with excess mortality, a key risk factor being cortisol deficiency due to ACTH deficiency[6]. The present study of cortisol secretory dynamics in hypothyroid men has shown elevated mean 24-h serum concentrations of cortisol with preserved circadian rhymicity and normal endogenous production rates, but prolonged half-lives of cortisol disappearance[7]. Higher cortisol levels have been reported in acute heart failure and CHF with cardiac cachexia. Serum cortisol levels were a complementary and incremental cardiac event risk predictor in combination with BNP in patients with chronic heart failure and that cardiac event prediction based on cortisol levels was influenced by oxidative stress[8]. It is possible to speculate that an increased cortisol secretion may contribute to worsening the metabolic control of diabetes and insulin sensitivity, consequently, inducing a higher prevalence of chronic diabetes complications[9].

TEST PRINCIPLE

Competitive chemiluminescence immunoassay.

The sample, ABEI labeled with Cortisol antigen, FITC labeled with Cortisol monoclonal antibody and magnetic microbeads coated with FITC antibody are mixed thoroughly and incubated. Cortisol released from the binding proteins in the serum or plasma sample by ANS, or cortisol present in the urine compete with Cortisol antigen labeled with ABEI for binding Cortisol monoclonal antibody labeled with FITC, forming immuno-complexes. The complexes are finally binding with magnetic microbeads coated with FITC antibody. After precipitation in a magnetic field, the supernatant is decanted and then a wash cycle is performed. Subsequently, the Starter 1+2 are added to initiate a chemiluminescent reaction. The light signal is measured by a photomultiplier as relative light units (RLUs), which is inversely proportional to the concentration of Cortisol present in the sample.

REAGENTS

Kit Contents

Component	Description	100 tests/kit	50 tests/kit	30 tests/kit
Magnetic Microbeads	Magnetic microbeads coated with FITC antibody (~50.0 μg/mL) in PBS buffer, NaN_3 (<0.1%).	2.5 mL	1.5 mL	1.0 mL
Calibrator Low	A low concentration of Cortisol antigen in PBS buffer, NaN_3 (<0.1%).	1.0 mL	1.0 mL	1.0 mL
Calibrator High	A high concentration of Cortisol antigen in PBS buffer, NaN_3 (<0.1%).	1.0 mL	1.0 mL	1.0 mL
FITC Label	FITC labeled with Cortisol monoclonal antibody (~71.4 ng/mL) in Tris-HCl buffer, NaN_3 (<0.1%).	5.5 mL	3.5 mL	2.7 mL
ABEI Label	ABEI labeled with Cortisol antigen (~83.3 ng/mL) in PBS buffer, ANS, NaN_3 (<0.1%).	6.5 mL	4.0 mL	3.0 mL
Control 1	A low concentration of Cortisol antigen (100 ng/mL) in PBS buffer, NaN_3 (<0.1%).	1.0 mL	1.0 mL	1.0 mL
Control 2	A high concentration of Cortisol antigen (300 ng/mL) in PBS buffer, NaN_3 (<0.1%).	1.0 mL	1.0 mL	1.0 mL
All reagents are provided ready-to-use.				

Warnings and Precautions

- For *in vitro* diagnostic use.
- For professional use only.
- Exercise the normal precautions required for handling all laboratory reagents.
- Personal protective measures should be taken to prevent any part of the human body from contacting samples, reagents, and controls, and should comply with local operating requirements for the assay.
- A skillful technique and strict adherence to the package insert are necessary to obtain reliable results.
- Do not use kit beyond the expiration date indicated on the label.
- Do not interchange reagent components from different reagents or lots.
- Avoid foam formation in all reagents and sample types (specimens, calibrators and controls).
- All waste associated with biological samples, biological reagents and disposable materials used for the assay should be considered potentially infectious and should be disposed of in accordance with local guidelines.
- This product contains sodium azide. Sodium azide may react with lead or copper plumbing to form highly explosive metal azides. Immediately after disposal, flush with a large volume of water to prevent azide build-up. For additional information, see Safety Data Sheets available for professional user on request.

Note: If any serious incident has occurred in relation to the device, please report to Shenzhen New Industries Biomedical Engineering Co., Ltd. (Snibe) or our authorized representative and the competent authority of the Member State in which you are established.

Reagent Handling

- To avoid contamination, wear clean gloves when operating with a reagent kit and sample. When handling reagent kit, replace the gloves that have been in contact with samples, since introduction of samples will result in unreliable results.
- Do not use kit in malfunction conditions; e.g., the kit leaking at the sealing film or elsewhere, obviously turbid or precipitation is found in reagents (except for Magnetic Microbeads) or control value is out of the specified range repeatedly. When kit in malfunction conditions, please contact Snibe or our authorized distributor.
- To avoid evaporation of the liquid in the opened reagent kits in refrigerator, it is recommended that the opened reagent kits to be sealed with reagent seals contained within the packaging. The reagent seals are single use, and if more seals are needed, please contact Snibe or our authorized distributor.
- Over time, residual liquids may dry on the septum surface. These are typically dried salts and have no effect on assay efficacy.
- Use always the same analyzer for an opened reagent integral.
- For magnetic microbeads mixing instructions, refer to the Preparation of the Reagent section of this package insert.
- For further information about the reagent handing during system operation, please refer to Analyzer Operating Instructions.

Storage and Stability

- Do not freeze the integral reagents.
- Store the reagent kit upright to ensure complete availability of the magnetic microbeads.
- Protect from direct sunlight.

Stability of the Reagents	
Unopened at 2-8°C	until the stated expiration date
Opened at 2-8°C	6 weeks
On-board	4 weeks

Stability of Controls	
Unopened at 2-8°C	until the stated expiration date
Opened at 10-30°C	6 hours
Opened at 2-8°C	6 weeks
Frozen at -20°C	3 months
Frozen and thawed cycles	no more than 3 times

SPECIMEN COLLECTION AND PREPARATION

Specimen Types

Only the specimens listed below were tested and found acceptable.

Specimen Types	Collection Tubes
Serum	Tubes without additive/accessory, or tubes containing clot activator or clot activator with gel.
Plasma	K2-EDTA
Urine	/

- The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. Follow tube manufacturers' instructions carefully when using collection tubes.

Specimen Conditions

- Do not use heat-inactivated samples or grossly hemolyzed/hyperlipidaemia specimens and specimens with obvious microbial contamination.
- Ensure that complete clot formation in serum specimens has taken place prior to centrifugation. Some serum specimens, especially those from patients receiving anticoagulant or thrombolytic therapy, may exhibit increased clotting time. If the serum specimen is centrifuged before a complete clotting, the presence of fibrin may cause erroneous results.
- Samples must be free of fibrin and other particulate matter.
- To prevent cross contamination, use of disposable pipettes or pipette tips are recommended.
- Due to the circadian rhythm of cortisol levels in serum and plasma, the sample collection time must be noted.
- Collect fresh urine into a clean container within 24 hours, there should be no antiseptic substance inside it, or add 10g boric acid into the urine sample by each liter.
- If the urine sample is cloudy or has a precipitate, centrifuge the sample and use the supernate in the assay.

Preparation for Analysis

- Inspect all specimens for foam. Remove foam with an applicator stick before analysis. Use a new applicator stick for each specimen to prevent cross contamination.
- Frozen specimens must be completely thawed before mixing. Mix thawed specimens thoroughly by low speed vortexing or by gently inverting. Visually inspect the specimens. If layering or stratification is observed, mix until specimens are visibly homogeneous. If specimens are not mixed thoroughly, inconsistent results may be obtained.
- Specimens should be free of fibrin, red blood cells, or other particulate matter. Such specimens may give reliable results and must be centrifuged prior to testing. Transfer clarified specimen to a sample cup or secondary tube for testing. For centrifuged specimens with a lipid layer, transfer only the clarified specimen and not the lipemic material.
- The sample volume required for a single determination of this assay is 40 μL.

Specimen Storage

Specimens removed from the separator, red blood cells or clot may be stored up to 24 hours at 10-30°C or 4 days at 2-8°C, or 12 months frozen at -20°C. Frozen specimens subjected to up to 2 freeze/thaw cycles have been evaluated.

Urine samples may be stored up to 48 hours at 10-30°C or 7 days at 2-8°C, or 3 months frozen at -20°C. Frozen specimens subjected to up to 3 freeze/thaw cycles have been evaluated.

Specimen Shipping

- Package and label specimens in compliance with applicable local regulations covering the transport of clinical specimens and infectious substances.
- Do not exceed the storage limitations listed above.

Specimen Dilution

- Samples, with Cortisol concentrations above the analytical measuring interval, can be diluted with manual dilution procedure. The recommended dilution ratio is 1:10. The concentration of the diluted sample must be >60 ng/mL.
- For manual dilution, multiply the result by the dilution factor.
- Please choose applicable diluents or ask Snibe for advice before manual dilution.

PROCEDURE

Materials Provided

Cortisol (CLIA) assay, control barcode labels.

Materials Required (But Not Provided)

- General laboratory equipment.
- Fully-auto chemiluminescence immunoassay analyzer Maglumi 600, Maglumi 800, Maglumi 1000, Maglumi 2000, Maglumi 2000 Plus, Maglumi 4000, Maglumi 4000 Plus, MAGLUMI X8, MAGLUMI X3, MAGLUMI X6 or Integrated System Biolumi 8000, Biolumi CX8.
- Additional accessories of test required for the above analyzers include Reaction Module, Starter 1+2, Wash Concentrate, Light Check, Tip, and Reaction Cup. Specific accessories and accessories' specification for each model refer to corresponding Analyzer Operating Instructions.
- Please use accessories specified by Snibe to ensure the reliability of the test results.

Assay Procedure

Preparation of the Reagent

- Take the reagent kit out of the box and visually inspect the integral vials for leaking at the sealing film or elsewhere. If there is no leakage, please tear off the sealing film carefully.
- Open the reagent area door; hold the reagent handle to get the RFID label close to the RFID reader (for about 2s); the buzzer will beep; one beep sound indicates successful sensing.
- Keeping the reagent straight insert to the bottom along the blank reagent track.
- Observe whether the reagent information is displayed successfully in the software interface, otherwise repeat the above two steps.
- Resuspension of the magnetic microbeads takes place automatically when the kit is loaded successfully, ensuring the magnetic microbeads are totally resuspended homogenous prior to use.

Assay Calibration

- Select the assay to be calibrated and execute calibration operation in reagent area interface. For specific information on ordering calibrations, refer to the calibration section of Analyzer Operating Instructions.
- Execute recalibration according to the calibration interval required in this package insert.

Quality Control

- When new lot used, check or edit the quality control information.
- Scan the control barcode, choose corresponding quality control information and execute testing. For specific information on ordering quality controls, refer to the quality control section of the Analyzer Operating Instructions.

Sample Testing

- After successfully loading the sample, select the sample in interface and edit the assay for the sample to be tested and execute testing. For specific information on ordering patient specimens, refer to the sample ordering section of the Analyzer Operating Instructions.

To ensure proper test performance, strictly adhere to Analyzer Operating Instructions.

Calibration

Traceability: This method has been standardized against the Snibe internal reference standard.

Test of assay specific calibrators allows the detected relative light unit (RLU) values to adjust the master curve.

Recalibration is recommended as follows:

- Whenever a new lot of Reagent or Starter 1+2 is used.
- Every 28 days.

- The analyzer has been serviced.
- Control values lie outside the specified range.

Quality Control

Controls are recommended for the determination of quality control requirements for this assay and should be run in singlicate to monitor the assay performance. Refer to published guidelines for general quality control recommendations, for example Clinical and Laboratory Standards Institute (CLSI) Guideline C24 or other published guidelines[10].

Quality control is recommended once per day of use, or in accordance with local regulations or accreditation requirements and your laboratory's quality control procedures, quality control could be performed by running the Cortisol assay:

- Whenever the kit is calibrated.
- Whenever a new lot of Starter 1+2 or Wash Concentrate is used.

Controls are only applicable with MAGLUMI and Biolumi systems and only used matching with the same top seven LOT numbers of corresponding reagents. For each target value and range refer to the label.

The performance of other controls should be evaluated for compatibility with this assay before they are used. Appropriate value ranges should be established for all quality control materials used.

Control values must lie within the specified range, whenever one of the controls lies outside the specified range, calibration should be repeated and controls retested. If control values lie repeatedly outside the predefined ranges after successful calibration, patient results must not be reported and take the following actions:

- Verify that the materials are not expired.
- Verify that required maintenance was performed.
- Verify that the assay was performed according to the package insert.
- If necessary, contact Snibe or our authorized distributors for assistance.

If the controls in kit are not enough for use, please order Cortisol (CLIA) Controls (REF: 160201468MT) from Snibe or our authorized distributors for more.

RESULTS

Calculation

The analyzer automatically calculates the Cortisol concentration in each sample by means of a calibration curve which is generated by a 2-point calibration master curve procedure. The results are expressed in ng/mL. For further information please refer to the Analyzer Operating Instructions.

Interpretation of Results

The expected range for the Cortisol assay was obtained by testing 1682 apparently healthy individuals in China, gave the following expected value:

Specimen Type	Specimen Collection	n	2.5th-97.5th percentiles (ng/mL)	Specimen Type	n	2.5th-97.5th percentiles (μg/24-hour)
Serum	6:00-10:00	568	45.5-208.2	Urine	541	53-385
	16:00-20:00	573	25.2-124.5			

μg/24-hour=(Concentration in ng/mL)×(Volume of urine excreted in milliliter per 24 hours)×10^{-3}.

Results may differ between laboratories due to variations in population and test method. It is recommended that each laboratory establish its own reference interval.

LIMITATIONS

- Results should be used in conjunction with patient's medical history, clinical examination and other findings.
- If the Cortisol results are inconsistent with clinical evidence, additional testing is needed to confirm the result.
- 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[11,12]. Additional information may be required for diagnosis.
- Heterophilic antibodies in human serum 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[13].
- Bacterial contamination or heat inactivation of the specimens may affect the test results.
- Due to the diurnal variation of cortisol levels in normal subjects, all serum cortisol measurements should be referenced to the time of day of sample collection.
- Pregnancy, contraceptives and estrogen therapy give rise to elevated cortisol concentrations.
- Samples obtained from patients being treated with prednisolone or prednisone may show falsely elevated cortisol levels. Caution must therefore be exercised with cortisol determinations for patients undergoing therapy with these and structurally related synthetic corticosteroids.

SPECIFIC PERFORMANCE CHARACTERISTICS

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

Precision

Precision was determined using the assay, samples and controls in a protocol (EP05-A3) of the CLSI (Clinical and Laboratory Standards Institute): duplicates at two independent runs per day for 5 days at three different sites using three lots of reagent kits (n = 180). The following results were obtained:

Sample	Mean (ng/mL) (n=180)	Within-Run		Between-Run		Reproducibility	
		SD (ng/mL)	%CV	SD (ng/mL)	%CV	SD (ng/mL)	%CV
Serum Pool 1	60.353	1.860	3.08	0.606	1.00	2.136	3.54
Serum Pool 2	361.574	7.185	1.99	4.623	1.28	14.118	3.90
Serum Pool 3	493.522	7.174	1.45	4.432	0.90	12.935	2.62
Plasma Pool 1	59.932	1.714	2.86	1.102	1.84	2.602	4.34
Plasma Pool 2	358.808	6.566	1.83	4.904	1.37	12.117	3.38
Plasma Pool 3	504.525	7.387	1.46	3.935	0.78	13.745	2.72
Urine Pool 1	20.243	0.618	3.05	0.424	2.09	0.936	4.62
Urine Pool 2	259.594	5.883	2.27	3.388	1.31	9.795	3.77
Urine Pool 3	492.874	6.974	1.41	3.780	0.77	11.222	2.28
Control 1	99.567	2.754	2.77	1.019	1.02	4.470	4.49
Control 2	302.685	7.226	2.39	3.303	1.09	11.047	3.65

Linear Range

4.00-600 ng/mL (defined by the Limit of Quantitation and the maximum of the master curve).

Reportable Interval

2.00-6000 ng/mL (defined by the Limit of Detection and the maximum of the master curve×Recommended Dilution Ratio).

Analytical Sensitivity

Limit of Blank (LoB) =0.500 ng/mL.
Limit of Detection (LoD) =2.00 ng/mL.
Limit of Quantitation (LoQ) =4.00 ng/mL.

Analytical Specificity

Interference

Interference was determined using the assay, three samples containing different concentrations of analyte were spiked with potential endogenous and exogenous interferents in a protocol (EP7-A2) of the CLSI. The measurement deviation of the interference substance is within ±10%. The following results were obtained:

Specimen Type	Interference	No interference up to	Interference	No interference up to
Serum	Hemoglobin	3000 mg/dL	IgM	10 mg/mL
	Intralipid	3000 mg/dL	IgA	10 mg/mL
	Bilirubin	60 mg/dL	K2-EDTA	22.75 μmol/mL
	HAMA	40 ng/mL	Prednisone	1000 μg/dL
	ANA	398 AU/mL	Dexamethasone	1000 μg/dL
	Rheumatoid factor	2000 IU/mL	Cortisone	1000 μg/dL
	Biotin	0.5 mg/dL	Fludrocortisone	10 μg/mL
	Total protein	10 g/dL	Spironolactone	10 μg/mL
	IgG	50 mg/mL		
Urine	Hemoglobin	3000 mg/dL	Creatinine	5 mmol/L
	Intralipid	3000 mg/dL	Urea	350 mmol/L
	Bilirubin	60 mg/dL	Dextrose	5 mmol/L
	Total protein	1000 mg/dL	Sodium chloride	1000 mmol/L

Cross-Reactivity

Cross-reactivity was determined using the assay, three samples containing different concentrations of analyte were spiked with potential cross-reactant in a protocol (EP7-A2) of the CLSI. The measurement deviation of the interference substance is within ±10%. The following results were obtained:

Specimen Type	Cross-reactant	No interference up to	Cross-reactant	No interference up to
Serum	Adrenalone HCl Hydrate	100 μg/dL	Progesterone	1000 μg/dL
	Corticosterone	100 μg/dL	Tetrahydrocortisone	1000 μg/dL
	11-Deoxy Corticosterone	1000 μg/dL	Testosterone	100 ng/mL
	11-Deoxy Cortisol	100 μg/dL	Androstenedione	100 ng/mL
	17α-Hydroxy Progesterone	1000 μg/dL		
Urine	Aldosterone	1000 μg/dL	17α-Hydroxy Progesterone	1000 μg/dL
	Adrenalone HCl Hydrate	100 μg/dL	Progesterone	1000 μg/dL
	Corticosterone	100 μg/dL	Tetrahydrocortisone	1000 μg/dL
	11-Deoxy Corticosterone	1000 μg/dL	Testosterone	100 ng/mL
	11-Deoxy Cortisol	100 μg/dL	Androstenedione	100 ng/mL

Method Comparison

A comparison of the Cortisol assay with a commercially available immunoassay, gave the following correlations:

Specimen Type	n	Passing-Bablok	Range of clinical specimen concentrations (ng/mL)
Serum	116	$\hat{y}$=1.0029x-0.6827, τ=0.959	4.76 - 581.4
Urine	119	$\hat{y}$=1.0029x-0.3583, τ=0.948	4.67 - 597.05

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SYMBOLS EXPLANATIONS

	Consult instructions for use		Manufacturer
8°C 2°C	Temperature limit (Store at 2-8°C)		Use-by date
Σ	Contains sufficient for<n> tests		Keep away from sunlight
	This way up	EC REP	Authorized representative in the European Community
IVD	*In vitro* diagnostic medical device	CONTENTS	Kit component
REF	Catalogue number	LOT	Batch code
CE	CE marking		

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