VIDAS® Cortisol S (CORS)

IVD

VIDAS® Cortisol S is an automated quantitative test for use on the VIDAS family instruments, for the quantitative determination of cortisol in human serum, plasma (lithium heparin or EDTA) or urine using the ELFA technique(Enzyme Linked Fluorescent Assay).
The VIDAS Cortisol S test aids in diagnosing or treating adrenocortical disorders.

SUMMARY AND EXPLANATION

Glucocorticoids are synthesized in the adrenal cortex and cortisol is the main glucocorticoid (1, 2). The concentration of serum cortisol is principally regulated by a negative feedback mechanism which controls the release of ACTH (adrenocorticotropic hormone) (3).
The amount of circulating cortisol is normally subject to a circadian rhythm: the levels of cortisol are highest early in the morning and return to a minimum around midnight (4).
Cortisol has a half-life of 60 to 70 minutes; it mainly circulates bound (90%) to a carrier protein called transcortin. Cortisol affects the carbohydrate, protein and lipidic metabolisms; it also regulates water and electrolyte retention. Corticotropic disorders lead to adrenal hyper or hypofunction, resulting in hyper or hypocorticism Hypercorticism may be connected with hyper-secretion of cortisol (adrenocortical tumor, Cushing's corticotropic adenoma), or result from corticotherapy (5, 6).
Hypocorticism is observed in cases of adrenal insufficiency, caused either by the failure of the adrenal gland to secrete sufficient quantities of hormones (Addison's disease), or by insufficient production of ACTH.

PRINCIPLE

VIDAS Cortisol S is an automated assay for the VIDAS system, which enables cortisol in human serum or plasma to be directly quantitatively measured.
The assay of urine samples (collected over a 24-hour period) is performed after extracting the cortisol with dichloromethane.
The assay principle combines the enzyme immunoassay competition method with a final fluorescent detection (ELFA).
The Solid Phase Receptacle (SPR®) serves as the solid phase as well as the pipetting device. Reagents for the assay are ready-to-use and pre-dispensed in the sealed reagent strips.
All of the assay steps are performed automatically by the instrument. The reaction medium is cycled in and out of the SPR several times.
The sample is transferred into the well containing the conjugate: alkaline phosphatase-labeled cortisol derivative. The cortisol in the sample will compete with the cortisol derivative in the conjugate for sites on the specific anti-cortisol antibody which is fixed onto the interior of the SPR.
During the final detection step, the substrate (4-Methyl-umbelliferyl phosphate) is cycled in and out of the SPR. The conjugate enzyme catalyzes the hydrolysis of this substrate into a fluorescent product (4-Methyl-umbelliferone), the fluorescence of which is measured at 450 nm. The intensity of the fluorescence is inversely proportional to the concentration of antigen present in the sample.
At the end of the assay, the results are automatically calculated by the instrument in relation to the calibration curve stored in memory, and then printed out.

CONTENT OF THE KIT (60 TESTS):

60 CORS strips	STR	Ready-to-use.
60 CORS SPRs 2 x 30	SPR	Ready-to-use. Interior of SPR coated with polyclonal anti-cortisol immunoglobulins (rabbit).
CORS control 1 x 2 mL (liquid)	C1	Ready-to-use. Human serum* + cortisol + 1 g/L sodium azide. MLE data indicate the confidence interval in ng/ml (“Control C1 Dose Value Range”).
CORS calibrator 2 x 3 mL (liquid)	S1	Ready-to-use. Human serum* + cortisol + 1 g/L sodium azide. MLE data indicate the concentration in ng/ml (“Calibrator (S1) Dose Value”) and the confidence interval in "Relative Fluorescence Value” (“Calibrator (S1) RFV Range”).
Specifications for the factory master data required to calibrate the test: • MLE data (Master Lot Entry) provided in the kit, or • MLE bar code printed on the box label.		
1 Package insert provided in the kit or downloadable from www.biomerieux.com/techlib.		

* This product has been tested and shown to be negative for HBs antigen, and antibodies to HIV1, HIV2 and HCV. However, since no existing test method can totally guarantee their absence, this product must be treated as potentially infectious. Therefore, usual safety procedures should be observed when handling.

The SPR

The SPR is coated during production with polyclonal anti-cortisol antibodies (rabbit). Each SPR is identified by the code “CORS”. Only remove the required number of SPRs from the pouch and **carefully reseal the pouch after opening**.

The reagent strip

The strip consists of 10 wells covered with a labeled, foil seal. The label comprises a bar code which mainly indicates the assay code, kit lot number and expiration date. The foil of the first well is perforated to facilitate the introduction of the sample. The last well of each strip is a cuvette in which the fluorometric reading is performed. The wells in the center section of the strip contain the various reagents required for the assay.

Description of the CORS strip

Wells	Reagents
1	Sample well.
2 - 3 - 4	Empty wells.
5	Conjugate: alkaline phosphatase-labeled cortisol derivative + releasing agent + 1 g/L sodium azide (600 µL).
6	Wash solution: Tris, NaCl (0.05 mol/L) pH 7.4 + 1 g/L sodium azide (600 µL).
7	Wash solution: Tris-Tween, NaCl (0.05 mol/L) pH 7.4 + 1 g/L sodium azide (600 µL).
8	Wash solution: DEA* (1.1 mol/L or 11.5 %) pH 9.8 + 1 g/L sodium azide (600 µL).
9	Empty well.
10	Reading cuvette with substrate: 4-Methyl-umbelliferyl phosphate (0.6 mmol/L) + diethanolamine (DEA**) (0.62 mol/L or 6.6%, pH 9.2) + 1 g/L sodium azide (300 µL).

* Signal Word: **DANGER**


Hazard statement

H318 : Causes serious eye damage.
H373 : May cause damage to organs through prolonged or repeated exposure.
H315 : Causes skin irritation.
H302 : Harmful if swallowed.

Precautionary statement

P280 :Wear protective gloves/protective clothing/eye protection/face protection.
P305 + P351 + P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
P309 + P311 : IF exposed or if you feel unwell: Call a POISON CENTER or doctor/physician.

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For further information, refer to the Material Safety Data Sheet.

REAGENTS, MATERIALS AND DISPOSABLES REQUIRED BUT NOT PROVIDED

- Pipette with disposable tip to dispense 100 µL, 150 µL and 1 mL.
- Powderless, disposable gloves.
- For other specific materials and disposables, please refer to the Instrument User’s Manual.
- Instrument of the VIDAS family.

For urine extraction procedure:
- Serum free (ref. 66 581),
- dichloromethane,
- polypropylene or polyethylene tubes,
- glass tubes.

WARNINGS AND PRECAUTIONS

- **For *in vitro* diagnostic use only.**
- **For professional use only.**
- **This kit contains products of human origin. No known analysis method can totally guarantee the absence of transmissible pathogenic agents. It is therefore recommended that these products be treated as potentially infectious and handled observing the usual safety precautions (see Laboratory Biosafety Manual - WHO - Geneva - latest Edition).**
- This kit contains products of animal origin. Certified knowledge of the origin and/or sanitary state of the animals does not totally guarantee the absence of transmissible pathogenic agents. It is therefore recommended that these products be treated as potentially infectious and handled observing the usual safety precautions (do not ingest or inhale).
- Do not use the SPRs if the pouch is pierced.
- Do not use visibly deteriorated STRs (damaged foil or plastic).
- Do not use reagents after the expiration date indicated on the label.
- Do not mix reagents (or disposables) from different lots.
- Use **powderless gloves**, as powder has been reported to cause false results for certain enzyme immunoassay tests.
- Kit reagents contain sodium azide which can react with lead or copper plumbing to form explosive metal azides. If any liquid containing sodium azide is disposed of in the plumbing system, drains should be flushed with water to avoid build-up.
- The wash buffer (well 8) contains a harmful agent (diethanolamine 11.5%). Refer to the hazard statements "H" and the precautionary statements "P" above.
- The cuvette with substrate (well 10) contains an irritant agent (diethanolamine 6.6 Refer to the hazard statements "H" and the precautionary statements "P" above.
- Spills should be wiped up thoroughly after treatment with liquid detergent or a solution of household bleach containing at least 0.5% sodium hypochlorite. See the User's Manual for cleaning spills on or in the instrument. Do not autoclave solutions containing bleach.
- The instrument should be regularly cleaned and decontaminated (see the User's Manual).

STORAGE CONDITIONS

- Store the VIDAS Cortisol S kit at 2-8°C.
- **Do not freeze reagents.**
- **Store all unused reagents at 2-8°C.**
- After opening the kit, check that the SPR pouch is correctly sealed and undamaged. If not, do not use the SPRs.
- **Carefully reseal the pouch with the desiccant inside after use to maintain stability of the SPRs and return the complete kit to 2-8°C.**
- If stored according to the recommended conditions, all the components are stable until the expiration date indicated on the label.

SPECIMENS

Specimen type and collection:

Human serum, plasma (sodium heparin, EDTA) or urine collected over a 24-hour period (with or without boric acid).

Sample preparation

Follow the tube manufacturer's recommendations for use.
- Plain tubes: wait for samples to coagulate and **centrifuge** to eliminate fibrin.
- Frozen stored sample: after thawing, all these samples must be centrifuged.

Note: blood sampling tube results may vary from one manufacturer to another depending on the materials and additives used.
It is the responsibility of each laboratory to validate the type of sample tube used and to follow the manufacturer's recommendations for use.

Specimen stability

Samples can be stored at 2-8°C in stoppered tubes for up to 3 days; if longer storage is required, freeze the sera or plasma at -25 ± 6°C. A study performed on frozen samples over a period of 2 months showed that the quality of results is not affected. Two freeze/thaw cycles have been validated.

Stability of urine samples

Urine samples can be stored frozen at -25 ± 6°C for 14 days.

Sample-related interference

With serum or plasma

None of the following factors have been found to significantly influence this assay:
- hemolysis (after spiking samples with hemoglobin up to 300 µmol/L (monomer) or 484 mg/dL),
- lipemia (after spiking samples with lipids up to 30 g/L equivalent in triglycerides),
- bilirubinemia (after spiking samples with bilirubin up to 510 µmol/L or 30 mg/dL).

However, it is recommended not to use samples that are clearly hemolyzed, lipemic or icteric, and if possible to collect a new sample.

With urine

None of the following factors have been found to significantly influence this assay:
- presence of glucose (after spiking urines with glucose: up to 55 mmol/L or 990 mg/dL),
- proteinuria (after spiking urines with human albumin: up to 5 g/L),
- hemoglobinuria (after spiking urines with hemoglobin: up to 300 µmol/L (monomer) or 484 mg/dL),
- creatinuria (after spiking urines with creatinine: up to 265 mmol/L),
- presence of sodium chloride (after spiking urines with NaCl: up to 750 mmol/L),
- presence of urea (after spiking urines with urea: up to 830 mmol/L).

INSTRUCTION FOR USE

For complete instructions, see the User's Manual.
Reading VIDAS® Protocole Test Change (PTC) protocol data and MLE data

When using the assay for the first time:
With the external instrument barcode reader,
1. Scan the PTC barcode(s) at the end of the package insert. or downloadable from www.biomerieux.com/techlib. This reading allows VIDAS® PTC protocol data to be transferred to the instrument software for its update.
2. Scan the MLE data on the box label.

Note: If the MLE data have been read before the VIDAS® PTC protocol, read the MLE data again.

When opening a new lot of reagents:
Enter the specifications (or factory master data) into the instrument using the master lot entry (MLE) data.
If this operation is not performed before initiating the tests, the instrument will not be able to print results.

Note: the master lot data need only be entered once for each lot.

It is possible to enter MLE data **manually or automatically** depending on the instrument (refer to the User's Manual).

Calibration

Calibration, using the calibrator provided in the kit, must be performed each time a new lot of reagents is opened, after the master lot data have been entered. Calibration should then be performed every 14 days. This operation provides instrument-specific calibration curves and compensates for possible minor variations in assay signal throughout the shelf-life of the kit (see User's Manual).
The calibrator, identified by S1, must be tested **in triplicate.** The calibrator value must be within the set RFV "Relative Fluorescence Value" range. If this is not the case, recalibrate.

Procedure

Urine extraction procedure

24-hour urine testing is performed following extraction of cortisol by the dichloromethane. This urine extraction step eliminates certain interferences linked with the urine matrice.

Proceed as follows:

1. Prepare the required number of polypropylene (or polyethylene) tubes in the racks.
2. For each 24-hour old urine sample, homogenize and dispense 1 mL of the sample into each tube.
3. Add 1 mL of dichloromethane to each tube after having saturated the pipette tip with dichloromethane.
4. **Shake for 20 to 30 seconds using a vortex-type mixer.**
5. When the two phases have separated, aspirate the aqueous phase.
6. Carefully collect 150 µL of the organic layer (dichloromethane) using a saturated tip and place in a pre-marked glass tube.
7. Evaporate using a stream of air or nitrogen.
8. Dissolve each dry extract in 150 µL of "Serum free" (ref. 66 581) and leave to incubate for 30 minutes at room temperature. Shake immediately on a vortex-type mixer, and again before performing the assay.
9. Then apply the assay procedure given below.

Assay procedure

1. **Remove the required reagents from the refrigerator.**
2. Use one "CORS" strip and one "CORS" SPR for each sample, control or calibrator to be tested. **Make sure the storage pouch has been carefully resealed after the required SPRs have been removed.**
3. The test is identified by the "CORS" code on the instrument. The calibrator must be identified by "S1", and tested **in triplicate**. If the control needs to be tested, it should be identified by "C1".
4. Mix the calibrator, control and samples (serum, plasma, extracted urine) using a vortex-type mixer.
5. **For this test, the calibrator, control, and sample test portion is 100 µL.**
6. Insert the "CORS" SPRs and "CORS" strips into the instrument. Check to make sure the color labels with the assay code on the SPRs and the Reagent Strips match.
7. **Initiate the assay immediately.** All the assay steps are performed automatically by the instrument.
8. Reclose the vials and return them to 2–8°C after pipetting.
9. The assay will be completed within approximately 40 minutes. After the assay is completed, remove the SPRs and strips from the instrument.
10. Dispose of the used SPRs and strips into an appropriate recipient.

RESULTS AND INTERPRETATION

Once the assay is completed, results are analyzed automatically by the computer. Fluorescence is measured twice in the Reagent Strip's reading cuvette for each sample tested. The first reading is a background reading of the substrate cuvette before the SPR is introduced into the substrate. The second reading is taken after incubating the substrate with the enzyme remaining on the interior of the SPR. The RFV (Relative Fluorescence Value) is calculated by subtracting the background reading from the final result. This calculation appears on the result sheet.

The results are automatically calculated by the instrument using calibration curves which are stored by the instrument (4-parameter logistic model); the concentrations are expressed in ng/mL.

The VIDAS Cortisol S assay is calibrated against the ID-GCMS reference method (Isotope Dilution - Gas Chromatography Mass Spectrometry) (7).

Samples with concentrations greater than 650 ng/mL should be retested after dilution by 1/3 (1 volume of sample + 2 volumes of "Serum free" (ref. 66 581)). Multiply the result by the dilution factor to obtain the sample concentration.
To calculate the quantity of cortisol in urine in µg per 24 hours:

$$\mu g/24h = \frac{ng/mL \times mL \text{ of urine} / 24 \text{ hours}}{1000}$$

Interpretation of test results should be made taking into consideration the patient's history, and the results of any other tests performed.

QUALITY CONTROL

A control is included in each VIDAS Cortisol S kit.
This control must be performed immediately after opening a new kit to ensure that reagent performance has not been altered. Each calibration must also be checked using this control. The instrument will only be able to check the control value if it is identified by C1.
Results cannot be validated if the control value deviates from the expected values.

The urine extraction procedure must be validated by testing an in-house or a commercially available control with a known concentration.

Note

It is the responsibility of the user to perform Quality Control in accordance with any local applicable regulations.

LIMITATIONS OF THE METHOD

Levels of cortisol, which are artificially high owing to the cross reactivity of polyclonal anti-cortisol antibodies used in the test, may be obtained for patients treated with prednisolone or prednisone or for patients undergoing a metopirone test which generates an increase in 11-deoxycortisol.
Interference may be encountered with certain sera containing antibodies directed against reagent components. VIDAS Cortisol S assay results should be interpreted as part of a complete clinical evaluation.

RANGE OF EXPECTED VALUES

These figures are given as a guide; it is recommended that each laboratory establishes its own expected values from a rigorously selected population.

Conversion factor

nmol/L x 0.362 = ng/mL
ng/mL (µg/L) x 2.76 = nmol/L

Plasma or serum concentration

Cortisol levels follow a circadian rhythm, and it is therefore important to take into account the time of sample collection (4).

A study was performed using serum samples collected in the morning and the afternoon from healthy male (n=118) and female (n=121) subjects. The expected values, defined by the 95% confidence interval limits for results obtained with VIDAS Cortisol S on the population studied, are:

- **morning** (8-10 a.m.) on 118 healthy subjects: **54.94 – 287.56 ng/mL**.
- **afternoon** (4-7 p.m.) on 121 healthy subjects: **24.61 – 171.52 ng/mL**.

Urine concentration

The expected values, defined by the 95% confidence interval limits for results obtained with VIDAS Cortisol S using 58 24-hour urine samples collected from healthy male (n=28) and female (n=30) subjects, are:
9.66 – 120.63 µg / 24 hours.

PERFORMANCE

Studies performed using VIDAS Cortisol S gave the following results:

Measurement range

The measurement values of the VIDAS Cortisol S kit range from 2 to 650 ng/mL.

Detection limit

The analytical detection limit, defined as the smallest concentration of serum cortisol which is significantly different from the zero concentration with a probability of 95 %, is **2 ng/mL**.

The functional detection limit, defined as the measured concentration of serum cortisol with a 20% inter-lot variation coefficient, is obtained at **5.15 ng/mL**.

Precision

Five serum samples and five extracted urine samples were tested in duplicate in 10 different runs (2 runs per day) with 2 reagent lots on two instruments (N=80).
The repeatability (intra-run precision), inter-run reproducibility (inter-run precision) and the inter-lot reproducibility (total precision = intra-run, inter-run, inter-day, inter-instrument, inter-lot) were calculated using this protocol, based on the recommendations of NCCLS document EP5-A2:

		Intra-run precision		Inter-run precision		Total precision	
Sample	Mean concentration ng/mL	Standard deviation	CV (%)	Standard deviation	CV (%)	Standard deviation	CV (%)
Serum 1	20.09	1.41	7.02	1.41	7.02	2.61	12.98
Serum 2	39.37	2.95	7.50	2.95	7.50	3.69	9.38
Serum 3	125.68	7.04	5.60	8.16	6.49	9.33	7.42
Serum 4	332.27	27.40	8.25	31.77	9.56	33.30	10.02
Serum 5	517.64	34.03	6,57	37.91	7.32	42.21	8.15
Urine 1	17.65	1.32	7.48	1.47	8.33	2.79	15.81
Urine 2	49.27	3.11	6.32	3.11	6.32	3.96	8.03
Urine 3	96.30	5.72	5.94	6.36	6.60	7.17	7.45
Urine 4	221.92	16.85	7.59	17.04	7.68	17.35	7.82
Urine 5	530.85	41.67	7.85	41.67	7.85	43.97	8.28

Specificity

During the study performed, the 50% displacement, in comparison with the zero standard, was calculated using dose-response curves for the tested components and the calibration curve for cortisol. The following results were obtained:

Tested compounds	Cross-reactivity %
Prednisolone	30
11-Deoxycortisol	8.7
Cortisone	4.2
Prednisone	2
6-methyl prednisolone	1.8
Corticosterone	1.4
21-deoxycortisol	1.2
11-deoxycorticosterone	0.33
17-hydroxyprogesterone	0.18
Dexamethasone	<0.1
Tetrahydrocortisol	<0.1
Tetrahydrocortisone	<0.1
Progesterone	<0.1
Testosterone	<0.1

Accuracy

3 samples were diluted in "Serum free" (ref. 66 581) and tested singly in 3 runs. The ratio of the mean concentration measured over the expected concentration is expressed as a mean recovery percentage.

Samples	Dilution factor	Mean measured concentration (ng/mL)	Mean expected concentration (ng/mL)	Mean recovery percentage (%)
1	pur	154.92	154.92	100.0
	3/4	116.86	116.19	100.6
	2/3	102.08	103.28	98.8
	1/2	68.96	77.46	89.0
	1/3	41.59	51.64	80.5
2	pur	291.23	291.23	100.0
	3/4	220.77	218.43	101.1
	2/3	191.67	194.16	98.7
	1/2	127.73	145.62	87.7
	1/3	83.32	97.08	85.8
3	pur	570.43	570.43	100.0
	3/4	432.91	427.83	101.2
	2/3	382.08	380.29	100.5
	1/2	297.55	285.22	104.3
	1/3	186.39	190.14	98.0

Comparison with the ID-GCMS reference method

64 serum samples, including the European Reference Material ERM®-DA451/IFCC panel, were tested using VIDAS Cortisol S and the ID-GCMS reference method (X). The comparison between the two methods was analyzed using the coefficient of correlation and the Passing & Bablok method:

Coefficient of correlation: r = 0.99
VIDAS Cortisol S = 0.976X + 1.154

Comparison with another test method

- 210 serum samples, spread over the measuring range, were tested in parallel using VIDAS Cortisol S and another commercially available kit (X). The comparison between the two methods was analyzed using the coefficient of correlation and the Passing & Bablok method:

  Coefficient of correlation: r = 0.95
  VIDAS Cortisol S = 0.877X + 7.308

- 110 urine samples, ranging between 4.63 and 409.18 ng/mL, were tested in parallel using VIDAS Cortisol S with an extraction step, and another commercially available kit (X) without an extraction step. The comparison between the two methods was analyzed using the coefficient of correlation and the Passing & Bablok method:

  Coefficient of correlation: r = 0.78
  VIDAS Cortisol S = 0.456X – 1.457

WASTE DISPOSAL

Dispose of used or unused reagents as well as any other contaminated disposable materials following procedures for infectious or potentially infectious products.
It is the responsibility of each laboratory to handle waste and effluents produced according to their nature and degree of hazardousness and to treat and dispose of them (or have them treated and disposed of) in accordance with any applicable regulations.

LITERATURE REFERENCES

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INDEX OF SYMBOLS

– Symbol	Meaning
REF	Catalog number
IVD	*In Vitro* Diagnostic Medical Device
	Manufacturer
	Temperature limit
	Use by date
LOT	Batch code
	Consult Instructions for Use
	Contains sufficient for <n> tests
	Date of manufacture

WARRANTY

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REVISION HISTORY

Change type categories :

N/A	Not applicable (First publication)
Correction	Correction of documentation anomalies
Technical change	Addition, revision and/or removal of information related to the product
Administrative	Implementation of non-technical changes noticeable to the user

Note: *Minor typographical, grammar, and formatting changes are not included in the revision history.*

Release date	Part Number	Change Type	Change Summary
2015/01	13414F	Administrative	INDEX OF SYMBOLS REVISION HISTORY
		Technical	CONTENT OF THE KIT (60 TESTS) WARNINGS AND PRECAUTIONS INSTRUCTIONS FOR USE

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