510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K202136

B Applicant

Immunodiagnostic Systems Ltd.

C Proprietary and Established Names

IDS Cortisol

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
CGR	Class II	21 CFR 862.1205 - Cortisol (Hydrocortisone And Hydroxycorticosterone) Test System	CH - Clinical Chemistry

II Submission/Device Overview:

A Purpose for Submission:

New device.

B Measurand:

Cortisol

C Type of Test:

Quantitative Immunoassay

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

The IDS Cortisol assay is an in vitro diagnostic device intended for the quantitative determination of cortisol in human serum and plasma on the IDS system. Results are to be used in conjunction with other clinical and laboratory data to assist clinicians in the diagnosis and treatment of disorders of the adrenal gland.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

IDS-iSYS Multi-Discipline Automated System, i.e. IDS system

IV Device/System Characteristics:

A Device Description:

The IDS Cortisol assay consists of a reagent cartridge. The reagent cartridge contains multiple reagents:

- MPE1: Magnetic particles coated rat anti-mouse monoclonal antibody in a phosphate buffer with Proclin as preservative.
- CONJ: Cortisol coupled with an acridinium ester derivative in phosphate buffer with Proclin as a preservative.
- mAb: Mouse anti-cortisol monoclonal antibody in phosphate buffer with Proclin as a preservative.;
- BUF: HEPES buffer containing Proclin as preservative.

B Principle of Operation:

The assay is based on chemiluminescence technology. 30µL of patient sample, controls or calibrators are incubated with assay buffer. Following the first incubation step, an anti-cortisol monoclonal antibody is added, followed by a subsequent incubation step. An acridinium labelled cortisol conjugate and anti-IgG antibody coated magnetic particles are added prior to a third incubation step. The magnetic particles are captured using a magnet and a wash step performed to remove any unbound analyte. Trigger reagents are added; the resulting light emitted by the acridinium label is inversely proportional to the concentration of analyte in the original sample.

V *Substantial Equivalence Information:*

A Predicate Device Name(s):
Elecsys Cortisol II

B Predicate 510(k) Number(s):
K152227

C Comparison with Predicate(s):

Device & Predicate Device(s):	K202136	K152227
Device Trade Name	IDS Cortisol	Elecsys Cortisol II
General Device Characteristic Similarities		
Intended Use	For quantitative determination of Cortisol	same
Sample Type	Human serum and plasma	same
Method of detection (Test methodology)	Chemiluminescence	same
General Device Characteristic Differences		
Sample Volume	30 µL	10 µL
Range of assay	0.59 – 45 µg/dL	3 – 1750 nmol/L (0.109 to 63.4 µg/dL)

VI Standards/Guidance Documents Referenced:

CLSI EP05-A3: Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline

CLSI EP06-A: Evaluation of the Linearity of Quantitative Measurement Procedures; Approved Guideline

CLSI EP07-A3: Interference Testing in Clinical Chemistry; Approved Guideline

CLSI EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline; Approved Guideline

EP28-A3C Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

The IDS Cortisol assay precision was evaluated internally in accordance with a modified protocol based on CLSI EP05-A3, "Evaluation of Precision Performance of Quantitative Measurement Methods." Six samples (two native serum samples and four contrived serum samples) were included in the precision testing at one site. Each of the six samples were tested for 20 days, two runs per day in two replicates using three lots of reagents on three IDS systems, one kit lot per system, with two operators. The IDS Cortisol assay precision was established using samples with concentrations ranging from approximately 0.80 µg/dL to 45.00 µg/dL.

Results from one representative lot on one IDS-iSYS system:

Sample	N	Mean Conc. (µg/dL)	Repeatability (Within run)		Reproducibility (Within - laboratory)	
			SD	CV	SD	CV
Contrived Human Serum 1	80	0.94	0.07	7.8%	0.15	16.2%
Native Human Serum 1	80	1.84	0.08	4.6%	0.20	10.9%
Contrived Human Serum 2	80	5.75	0.14	2.4%	0.30	5.2%
Contrived Human Serum 3	80	13.06	0.31	2.4%	0.52	3.9%
Native Human Serum 2	80	19.94	0.36	1.8%	1.02	5.1%
Contrived Human Serum 4	80	44.63	0.85	1.9%	1.89	4.2%

Results for the combined three lots on three IDS systems:

Sample	N	Mean Conc. (µg/dL)	Within run		Total	
			SD	CV	SD	CV
Contrived Human Serum 1	240	0.88	0.06	7.1%	0.14	15.3%

Sample	N	Mean Conc. (µg/dL)	Within run		Total	
			SD	CV	SD	CV
Native Human Serum 1	240	1.78	0.08	4.3%	0.18	10.1%
Contrived Human Serum 2	240	5.75	0.13	2.3%	0.26	4.5%
Contrived Human Serum 3	240	13.09	0.25	1.9%	0.43	3.3%
Native Human Serum 2	240	20.22	0.35	1.7%	0.96	4.8%
Contrived Human Serum 4	240	44.48	0.74	1.7%	2.22	5.0%

2. Linearity:

Linearity of the IDS Cortisol assay was conducted based on guidance from CLSI EP6-A. A high human serum sample (~45 µg/dL) and a low human serum sample (0.40 µg/dL) were prepared respectively by spiking a serum sample with a high concentration cortisol solution and diluting a serum sample with cortisol-free calibrator matrix. The high and low serum samples were mixed to create a total of 14 concentration levels. Samples were assayed in quadruplicate within a single run.

Statistical evaluation using linear regression showed that the assay is linear from 0.59 to 45.00 µg/dL, yielding a linear regression result of $y = 1.01x + 0.01$ with a correlation coefficient of $R^2 = 1.00$.

3. Analytical Specificity/Interference:

Endogenous and Exogenous Drug Interference:

Except for Rheumatoid Factor, interference was evaluated in accordance with CLSI EP07-A3 on two contrived serum samples at two different cortisol concentrations (~2 µg/dL to ~30 µg/dL). Interference substances were spiked into the serum samples and the results were measured and compared between the spiked and un-spiked samples. Each interferent was tested at two different levels. Both spiked and un-spiked samples were assayed in 26 replicates each. The sponsor defined significant interference as >10% bias between test and control samples.

To determine potential interference of Rheumatoid Factor, a serum sample with ~5 µg/dL cortisol and high Rheumatoid Factor concentration was diluted 1:2 and 1:4 in calibrator matrix and each dilution was assayed in duplicate. The recovery bias compared to the neat sample for each dilution was < 10%.

Potential Interferent	Highest Concentration of substance tested which demonstrated no significant interference
Acetaminophen	200 µg/mL
Bilirubin (Conjugated)	40 mg/dL
Bilirubin (Unconjugated)	40 mg/dL
Biotin	6 µg/mL
Carbamezapine	30 µg/mL
Haemoglobin	500 mg/dL
HAMA	1000 ng/mL
Ibuprofen	500 µg/mL
Phenytoin	50 µg/mL
Rheumatoid Factor (RhF)	2000 IU/mL
Total protein	12 g/dL
Triglycerides	3000 mg/dL

The package insert contains the following limitations:

Heterophilic antibodies in human serum can react with reagent immunoglobulins, interfering with in vitro immunoassays. Patients routinely exposed to animals or to animal serum products can be prone to this interference and anomalous values may be observed.

Pregnancy, contraceptives and estrogen therapy lead to elevated cortisol concentrations."

Cross-reactivity:

Cross-reactivity studies were performed in accordance with CLSI EP07- A3. Contrived serum samples were spiked with 13 potential cross-reactants. The analyte concentration of the samples was approximately ~2 and ~30 µg/dL of cortisol. For each serum sample spiked with a cross-reactant, a control (un-spiked sample) was prepared by replacing the cross-reactant with the same volume of cross-reactant solvent. Both spiked and un-spiked samples were assayed in 26 replicates each.

The percentage of cross reactivity was determined using the formula below:

$$\% \text{ cross reactivity} = \frac{(\text{Mean conc. of spiked sample} - \text{mean conc. of un-spiked sample})}{\text{Final concentration of cross-reactant added}} \times 100\%$$

Potential Cross Reactant	Tested Concentration	Highest cross-reactivity observed (%)
Cortisone	100 µg/dL	36.5
Corticosterone	100 µg/dL	19.9
Dexamethasone	1000 µg/dL	1.4
Prednisone	100 µg/dL	43.5
Prednisolone	50 µg/dL	51.3

Potential Cross Reactant	Tested Concentration	Highest cross-reactivity observed (%)
21-deoxycortisol	100 µg/dL	37.0
6-a-Methylprednisolone	10 µg/dL	-0.4
17-a-Hydroxyprogesterone	1000 µg/dL	2.6
6-b-Hydroxycortisol	100 µg/dL	0.4
Progesterone	1000 µg/dL	0.3
11-Deoxycortisol	100 µg/dL	11.5
11-Deoxycorticosterone	1000 µg/dL	2.2
Aldosterone	1000 µg/dL	0.0

The package insert contains the following limitations:

"In samples from patients who have been treated with prednisolone, methylprednisolone or prednisone may lead to falsely elevated cortisol concentrations.

Patients suffering from 21-hydroxylase deficiency exhibit elevated 21-deoxycortisol and this can also lead to elevated cortisol levels."

4. Assay Reportable Range:

The reportable range of the assay is 0.59 – 45.00 µg/dL. Any value that reads below 0.59 µg/dL should be reported as "<0.59 µg/dL". Any value that reads above 45.00 µg/dL should be reported as ">45.00 µg/dL." The results of the detection limit, linearity and method comparison studies support the assay reportable range.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

Traceability:

The IDS Cortisol assay is standardized against the ERM-DA451/IFCC panel, which is traceable to the LC-MS/MS Candidate Reference Measurement Procedure (cRMP) Total Serum Cortisol.

6. Detection Limit:

The limit of blank (LoB), limit of detection (LoD) and limit of quantitation (LoQ) were determined with guidance from CLSI EP17-A2, "Protocols for Determination of Limits of Detection and Limits of Quantitation" using 60 blank replicates and 13 low level samples. The LoB, LoD and LoQ samples were tested with three kit lots.

The limit of blank (LoB) was determined using zero calibrator matrix. Each LoB sample was assayed during a five-day period for a total of 60 replicates (12 replicates per assay, one assay per day, for five days) on one instrument by one operator for each kit lot. A different instrument was used for each kit lot. LoB was calculated according to the parametric function as described in CLSI EP17-A2.

The limit of detection (LoD) samples were prepared by diluting two human serum samples with zero matrix to achieve a panel of samples of six cortisol levels ranging from 0.21 to 0.71µg/dL. Each of the six LoD samples was measured in duplicate. For each kit lot, a total of ten assays were performed over a five-day period by one operator and on a different instrument per kit lot, for a total of ten replicates per sample. LoD was calculated according to CLSI EP17-A2.

The limit of quantitation (LoQ) samples were prepared by diluting two human serum samples with zero matrix to achieve 7 sample levels ranging from 0.21 to 1.21µg/dL. The LoQ panel of seven samples were measured in duplicate two times per day. For each kit lot, a total of ten assays were run over a five-day period by one operator and on a different instrument, for a total of 20 replicates per sample. The limit of quantitation was defined as the lowest analyte concentration with a within-laboratory precision of ≤ 20% CV.

LoB, LoD and LoQ were calculated according to the parametric analysis described in CLSI EP17-A2. The results support the following detection limits:

Sensitivity	**Concentration (µg/dL)**
Limit of Blank (LoB)	0.10
Limit of Detection (LoD)	0.24
Limit of Quantitation (LoQ)	0.59

7. Assay Cut-Off:

Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:

A method comparison study was performed by comparing the IDS Cortisol assay to the predicate device. A total of 194 serum samples (175 native and 19 contrived), with cortisol values ranging between 0.64 to 44.66 µg/dL, were tested internally.

Samples were tested in singlicate using one lot for the predicate device, Roche Elecsys Cortisol II, and in singlicate by the IDS Cortisol assay using one kit lot. The correlation data analysis was performed using Passing-Bablok regression.

n	**Slope**	**95% CI**	**Intercept (µg/dL)**	**95% CI**	**Correlation Coefficient (r)**
194	1.06	1.04 to 1.07	-0.10	-0.39 to 0.04	0.99

2. Matrix Comparison:

A matrix comparison study was performed to evaluate differences across tube types (serum separator tubes (SST), lithium heparin plasma, sodium heparin plasma, K2 EDTA plasma and K3 EDTA plasma) compared to control samples (red top serum, without additive). A total of 45 matched samples covering the range of 0.89 to 42.38 µg/dL were

tested. All 45 samples were analyzed over different assay runs using one kit lot on one instrument. Passing-Bablok regression analysis results are shown below:

Sample type	N	Slope	95% CI	Intercept (µg/dL)	95% CI	Corr. Coeff. (r)
SST	45	1.02	0.99 to 1.03	-0.08	-0.18 to 0.10	1.00
K_2 EDTA	45	1.03	1.01 to 1.04	-0.11	-0.23 to 0.03	1.00
K_3 EDTA	45	1.02	0.99 to 1.03	-0.10	-0.29 to 0.08	1.00
Lithium Heparin	45	1.00	0.99 to 1.02	0.15	-0.01 to 0.33	1.00
Sodium Heparin	45	1.01	1.00 to 1.03	0.00	-0.16 to 0.18	1.00

The results of this study support that the IDS Cortisol assay can be performed using serum (standard sampling tubes or tubes containing serum separating gel, SST) or plasma (lithium heparin, sodium heparin, K2 EDTA plasma and K3 EDTA plasma) samples.

C Clinical Studies:

1. Clinical Sensitivity:

   Not applicable

2. Clinical Specificity:

   Not applicable

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

   Not applicable

D Clinical Cut-Off:

Not applicable

E Expected Values/Reference Range:

The cortisol concentration was measured in serum samples collected from 307 apparently healthy donors using the IDS Cortisol assay. The study cohort included subjects from 21 to 65 years of age, with normal blood pressure (120/80) and normal body mass index, (18.5 to 29.0). Individuals who were pregnant, breast feeding, had personal history of chronic disease, under any prescription medication or any doctor prescribed diet were excluded from the study. The 95% reference intervals for apparently healthy adults were calculated by a non-parametric method following guidance from CLSI C28-A3 “Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory.”

	Morning hours 6 – 10 am	Afternoon hours 4 – 8 pm
Number of subjects	151	156
Mean (µg/dL)	11.6	7.46

	Morning hours 6 – 10 am	Afternoon hours 4 – 8 pm
SD (µg/dL)	3.88	2.81
Median (µg/dL)	11.3	7.15
Observed 2.5th to 97.5th percentile (µg/dL)	4.23-20.1	2.37-13.6

The sponsor states in the package insert "The above ranges should be considered as guidelines only; it is recommended that each laboratory establish its own expected range based upon its own patient population. The time of sample collection must be considered when interpreting results due to the cortisol secretion circadian rhythm. Severe stress can also lead to elevated cortisol levels."

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.