510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K223867

B Applicant

Immunodiagnostic Systems Limited

C Proprietary and Established Names

IDS ACTH II

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
CKG	Class II	21 CFR 862.1025 - Adrenocorticotropic Hormone (ACTH) Test System	CH - Clinical Chemistry

II Submission/Device Overview:

A Purpose for Submission:

New Device

B Measurand:

Adrenocorticotropic hormone (ACTH)

C Type of Test:

Quantitative electrochemiluminescence immunoassay

III Intended Use/Indications for Use:

A Intended Use(s):
See Indications for Use below.

B Indication(s) for Use:
IDS ACTH II assay is an automated in vitro diagnostic device intended for the quantitative, determination of ACTH in human K2 and K3 EDTA plasma on the IDS system. Results are to be used in conjunction with other clinical and laboratory data as an aid in the assessment of pituitary and adrenal gland function and the differential diagnosis of hyper- and hypo-cortisolism.

C Special Conditions for Use Statement(s):
Rx - For Prescription Use Only

D Special Instrument Requirements:

IDS-iSYS Multi-Discipline Automated Analyzer

IV Device/System Characteristics:

A Device Description:

Components of the candidate device include:

- Magnetic particles coated with mouse monoclonal anti-ACTH antibody and buffer containing phosphate with blocking proteins and ProClin 300 as preservative (<0.1%), 1 bottle, 2.5 mL
- Mouse monoclonal anti-ACTH antibody labeled with an acridinium ester derivative, in buffer containing phosphate with BSA and ProClin 300 as preservative (<0.1%), 1 bottle, 6.5 mL
- Buffer containing phosphate with blocking proteins and ProClin 300 as preservative (<0.1%), 1 bottle, 3.5 mL
- A mini-CD containing documentation

B Principle of Operation:

The assay is based on chemiluminescence technology. 150 µL of patient sample or calibrators are incubated with monoclonal anti-ACTH antibody-coated magnetic particles. Following the first incubation step, an acridinium-labeled ACTH antibody conjugate is added, followed by a subsequent incubation step. The magnetic particles are captured using a magnet, and a wash step is performed to remove any unbound analyte. Trigger reagents are added; the resulting light emitted by the acridinium label is proportional to the concentration of analyte in the original sample.

V Substantial Equivalence Information:

A Predicate Device Name(s):
Roche Elecsys- ACTH

B Predicate 510(k) Number(s):
K060585

C Comparison with Predicate(s):

Device & Predicate Device(s):	K223867	K060585
Device Trade Name	IDS ACTH II	Roche Elecsys - ACTH
General Device Characteristic Similarities		
Intended Use/	Quantitative determination of ACTH in human EDTA plasma	Same
Test Method	Electrochemiluminescence	Same
General Device Characteristic Differences		
Sample Type	K_2- and K_3-EDTA plasma	K_3-EDTA plasma
Measuring Range	4-1000 pg/mL	1-2000 pg/mL
Sample Volume	150 µL	50 µL

VI Standards/Guidance Documents Referenced:

CLSI EP05-A3: Evaluation of Precision of Quantitative Measurement Procedures

CLSI EP07, 3rd Ed.: Interference Testing in Clinical Chemistry

CLSI EP09c, 3rd Ed.: Measurement Procedure Comparison and Bias Estimation Using Patient Samples

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

CLSI EP28-A3c: Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory

CLSI EP35, 1st Ed.: Assessment of Equivalence or Suitability of Specimen Types for Medical Laboratory Measurement Procedures

CLSI EP37, 1st Ed.: Supplemental Tables for Interference Testing in Clinical Chemistry

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Precision studies were conducted using five K_3-EDTA plasma samples. Within-run precision was established by testing one reagent lot on one analyzer by two operators, over 20 days, with two runs per day and two replicates per run, for a total of 80 replicates per sample.

Reproducibility was established by testing one reagent lot by three operators, one operator per each of three analyzers, over five days, with five replicates per run, for a total of 75 replicates per sample. Lot-to-lot precision was established by testing three reagent lots on one analyzer by one operator, over five days, with five replicates per run, for a total of 75 replicates per sample.

The results of the 20-day precision study are shown in the table below.

Sample ID	N	Mean Conc. (pg/mL)	Repeatability		Within Laboratory	
			SD	CV%	SD	CV%
1	80	6	0.8	-	1.5	-
2	80	13	0.7	5.3%	1.6	12.8%
3	80	81	0.9	1.2%	2.5	3.1%
4	80	215	3.1	1.4%	5.3	2.5%
5	80	616	5.5	0.9%	10.5	1.7%

The results of the 5-day reproducibility studies are shown in the table below.

Reproducibility						
Sample ID	N	Mean Conc. (pg/mL)	Repeatability		Reproducibility	
			SD	CV%	SD	CV%
1	75	4	0.6	-	1.0	-
2	75	17	0.6	3.6%	1.2	7.2%
3	75	59	1.5	2.5%	3.5	6.0%
4	75	213	2.9	1.4%	9.3	4.4%
5	75	615	7.5	1.2%	27.8	4.5%

Lot-to-lot precision								
Sample ID	N	Mean Conc. (pg/mL)	Repeatability		Within Laboratory		Reproducibility	
			SD	CV%	SD	CV%	SD	CV%
1	75	4	0.8	-	1.4	-	2.0	-
2	75	17	0.7	4.1	0.9	5.5	1.8	10.9
3	75	61	0.8	1.3	1.5	2.5	1.9	3.2
4	75	217	1.7	0.8	4.1	1.9	7.6	3.5
5	75	645	3.8	0.6	7.3	1.1	31.8	4.9

2. Linearity:

The linearity study was performed with reference to the protocols in CLSI EP06-A2 using series dilutions by mixing different proportion of the high and low samples with four replicates per sample. The data was analyzed using a linear regression. The maximum deviation from linearity observed within the claimed measuring range was 11.1%. The results support the claimed measuring range of 4 to 1000 pg/mL.

3. Analytical Specificity/Interference:

The analytical specificity of the IDS ACTH II assay on the IDS-iSYS Multi-Discipline Automated Analyzer was established by conducting interference testing following the recommendations in CLSI EP07 third edition guideline.

Interference from endogenous and exogenous substances was assessed using plasma samples containing ACTH at 15 pg/mL and 200 pg/mL. Each sample was further divided into two aliquots: a test sample (with added interferent) and a control sample (with no added interferent). Each sample was tested in a minimum of 4 replicates. The difference between the mean concentration of the test and control sample were calculated. The following table lists the highest concentration of each substance at which no significant interference was found, defined as a difference of less than or equal to ±10% between the test sample and control.

Interferent	**Highest interferent concentration tested that showed no significant interference**
Triglycerides	1500 mg/dL
Hemoglobin	62.5 mg/dL
Bilirubin, unconjugated	40 mg/dL
Bilirubin, conjugated	40 mg/dL
Protein (total)	15 g/dL
Rheumatoid Factor	324 IU/mL
HAMA	1000 ng/mL
Biotin	3.5 µg/mL
Acetaminophen	15.6 mg/dL
Acetylsalicylic acid	3 mg/dL
Ampicillin	7.5 mg/dL
Ibuprofen	21.9 mg/dL
Dexamethasone	1.2 mg/dL
Metyrapone	1.8 mg/L

The following statements are included as limitations in the device labeling:

The lowest Hemoglobin level that does not significantly interfere (≤±10% bias) with the assay is 62.5 mg/dL. Visual hemolysis in the sample is typically already seen in samples with hemoglobin concentration of 50 mg/dL or greater [Hemolysis_Palette_Bookmark-P.pdf (cdc.gov)]. Visibly hemolyzed samples must not be used with IDS ACTH II assay.

As with all tests containing monoclonal mouse antibodies, erroneous findings may be obtained from samples taken from patients who have been treated with monoclonal mouse antibodies or who have received them for diagnostic purposes.

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.

The lowest Rheumatoid Factor (RF) level that does not significantly interfere (≤±10% bias) with IDS ACTH II assay is 324 IU/mL.

Cholesterol interference was assessed by testing plasma samples with ACTH concentrations of 30 and 500 pg/mL. Each sample was further divided into two aliquots: a test sample (with added interferent) and a control sample (with no added interferent). Each sample was tested in 5 replicates. The difference between the mean concentration of the test and control sample was calculated. The highest level tested that demonstrated no significant interference (<10%) was 400 mg/dL.

Cross-Reactivity: Cross-reactivity was evaluated by spiking structurally similar compounds described below into ACTH-free urine. The results are summarized in the table below. No significant cross-reactivity was observed in the following compounds at the indicated concentration.

Cross-Reactant	**Concentration of cross-reactant [pg/mL]**	**% Cross-reactivity**
POMC	500	-2.1%
	50,000	0.0%
	500,000	0.0%
B-endorphin	500	-2.9%
	50,000	0.0%
	500,000	0.0%
a-MSH	500	-3.7%
	50,000	-0.4%
	500,000	-0.1%
b-MSH	500	-4.6%
	50,000	0.0%
	500,000	0.0%
ACTH 1-17	500	-1.8%
	50,000	-0.6%
	500,000	-0.1%
ACTH 1-24	500	-5.8%
	50,000	-0.5%
	500,000	-0.1%
ACTH 18-39	500	-6.5%
	50,000	-0.3%
	500,000	-0.1%
ACTH 22-39	500	4.9%
	50,000	-0.4%
	500,000	-0.1%
ACTH 1-10	500	-7.5%
	50,000	-0.1%
	500,000	0.0%
ACTH 11-24	500	-7.3%
	50,000	-0.1%
	500,000	0.0%

Studies evaluating high-dose hook effect demonstrated that samples containing ACTH concentrations up to 3×10^6 pg/mL do not give falsely low results with this assay.

4. Assay Reportable Range:

   The assay measuring interval is 4-1000 pg/mL.

   The sponsor provided data to support that the measuring interval can be extended up to 1,500 mg/dL following manual dilution.

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

   The IDS ACTH II Calibrators are traceable to a commercially available ACTH assay.

6. Detection Limit:

   Limit of blank (LoB), limit of detection (LoD), and limit of quantitation (LoQ) were determined using three reagent lots on one analyzer over three days. LoB was established with four blank samples, five replicates, once per day for three days (n = 60 replicates/lot). LoD and LoQ were established with six low level samples tested on five replicates each, once per day for three days (n = 90 replicates/lot). The claimed LoB for the IDS ACTH II is 0 pg/mL and the claimed LoD is 1 pg/mL. LoQ was determined to be 3 pg/mL as the lowest concentration measured with a within-laboratory precision CV ≤ 20%.

7. Assay Cut-Off:

   Not Applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:

   A method comparison study was conducted comparing the IDS ACTH II assay (y) with the Roche Elecsys ACTH (x). A total of 170 samples were tested in duplicate using one lot of the IDS ACTH II device and tested in single replicate using one lot of the Elecsys ACTH. Only the first replicate of IDS ACTH II was used for data analysis. Data were analyzed using Passing Bablok regression analysis. Results are shown below:

N	Concentration range (pg/mL)	Intercept	Slope	Correlation Coefficient (R)
170	4-997	- 0.8587	1.013	0.98

2. Matrix Comparison:

Fifty-five (55) matched K2 and K3 EDTA samples were assayed in duplicates with IDS ACTH II assay. The first replicate result for each sample was used for the data analysis. Results were analyzed using Passing-Bablok regression analysis.

Matrix	n	Range tested(pg/mL)	r	slope	intercept
K2EDTA Plasma vs. K3EDTA Plasma	55	6 - 1228	1.00	1.027	1.859

The results demonstrate equivalency between K2EDTA plasma and K3EDTA plasma.

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:

A study was performed with IDS ACTH II device using K3 EDTA plasma samples from 140 healthy subjects aged between 21 to 80 years old. The 95 % reference interval was calculated by a non-parametric method following guidance from CLSI C28-A3.

The following reference range were determined and are provided in the labeling (2.5^{th} to 97.5^{th} percentile): 6 – 51 pg/mL

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.