510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number
K231927

B Applicant
Roche Diagnostics

C Proprietary and Established Names
Elecsys PTH, Elecsys PTH STAT

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
CEW	Class II	21 CFR 862.1545 - Parathyroid Hormone Test System	CH - Clinical Chemistry

II Submission/Device Overview:

A Purpose for Submission:
Modification of a cleared device

B Measurand:
Intact parathyroid hormone

C Type of Test:
Quantitative, electro-chemiluminescence (ECLIA) assay

III Intended Use/Indications for Use:

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

B Indication(s) for Use:
Immunoassay for the in vitro quantitative determination of intact parathyroid hormone in human serum and plasma for the differential diagnosis of hypercalcemia and hypocalcemia. This assay can be used intraoperatively.

The electrochemiluminescent immunoassay "ECLIA" is intended for use on Elecsys and cobas e immunoassay analyzers.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

For in vitro diagnostic use only
The sponsor has the following limitations in the Elecsys PTH Immunoassay regarding the hemoglobin interference:
Do not analyze samples that show visible signs of hemolysis.
The assay is affected by hemolysis > or equal to 0.10 g/dL.

The sponsor has the following limitations in the Elecsys PTH STAT Immunoassay regarding the hemoglobin interference:
Do not analyze samples that show visible signs of hemolysis.
The assay is affected by hemolysis > or equal to 0.25g/dL.

D Special Instrument Requirements:

Elecsys cobas e 601 analyzer

IV Device/System Characteristics:

A Device Description:

The Elecsys PTH and Elecsys PTH STAT immunoassays has been updated to account for biotin remediation by incorporating a biotinylated monoclonal PTH-specific antibody labeled with a ruthenium complex.

Each Rack Pack of PTH or PTH STAT reagent consists of the following:

-M Streptavidin coated microparticles (transparent cap), 1 bottle, 6.5 mL: Streptavidin coated microparticles 0.72 mg/mL; preservative.

-R1 Anti PTH Ab~biotin (gray cap), 1 bottle, 7 mL: Biotinylated monoclonal anti PTH antibody (mouse) 2.3 mg/L; phosphate buffer 100 mmol/L, pH 7.0; preservative.

-R2 Anti PTH Ab~Ru(bpy) (black cap), 1 bottle, 7 mL: Monoclonal anti PTH antibody (mouse) labeled with ruthenium complex 2.0 mg/L; phosphate buffer 100 mmol/L, pH 7.0; preservative.

B Principle of Operation:

The Elecsys PTH Assay is a two-step sandwich immunoassay with streptavidin microparticles and electrochemiluminescence detection. In the first incubation,50 µL of sample, a biotinylated monoclonal PTH-specific antibody, and monoclonal PTH-specific antibody labeled with a ruthenium complex form a sandwich complex. In the second incubation, after the addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin. It requires 50 µL of sample. Results are determined using a calibration curve that is generated specifically on each instrument by a 2 point calibration and a master curve provided with the reagent bar code. The assay time is 18 minutes.

The Elecsys PTH STAT Assay is a two-step sandwich immunoassay with streptavidin microparticles and electrochemiluminescence detection. A biotinylated monoclonal PTH-specific antibody, a monoclonal PTH-specific antibody labeled with a ruthenium complex and streptavidin-coated microparticles react to form a sandwich complex, which is bound to the solid phase. It requires 50 µL of sample. Results are determined using a calibration curve that is generated specifically on each instrument by a 2 point calibration and a master curve provided with the reagent bar code. The assay time is 9 minutes.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Elecsys PTH Immunoassay
Elecsys PTH STAT Immunoassay

B Predicate 510(k) Number(s):

K070709

C Comparison with Predicate(s):

Device & Predicate Device(s):	K231927	K070709
Device Trade Name	Elecsys PTH, Elecsys PTH STAT	Elecsys PTH Immunoassay, Elecsys PTH STAT Immunoassay
General Device Characteristic Similarities		
Intended Use	Immunoassay for the in vitro quantitative determination of intact parathyroid hormone in human serum and plasma for the differential diagnosis of hypercalcemia and hypocalcemia. This assay can be used intraoperatively.	Same
Assay Technology	Electrochemiluminescence	Same
General Device Characteristic Differences		
Sample matrix	Serum, K2-EDTA plasma, and K3-EDTA plasma	Serum and K3-EDTA plasma
Analytical Measuring Interval	1.20-5,000 pg/mL	6 pg/mL-5,000 pg/mL
Biotin Tolerance	Up to 1,200 ng/mL	Up to 50 ng/mL

VI Standards/Guidance Documents Referenced:

Clinical & Laboratory Standards Institute (CLSI) EP05-A3: Evaluation of Precision of Quantitative Measurement Procedures; Third Edition.

CLSI EP06: Evaluation of Linearity of Quantitative Measurement Procedures; Second Edition.

CLSI EP09c: Measurement Procedure Comparison and Bias Estimation using Patient Samples, Third Edition.

CLSI EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Second Edition.

CLSI EP07-A3, Interference Testing in Clinical Chemistry; Third Edition.

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Repeatability (within-run precision) and intermediate precision (within-laboratory precision) were evaluated following the recommendations in the CLSI EP05-A3 guideline.

Repeatability:
A repeatability study was performed using five pooled serum samples and three controls (PreciControl Varia indicated by PC V0, PC V1 and PC V2) with concentrations spanning the measuring range. Samples were tested in duplicate using 2 runs per day over 21 days for a total of 84 replicates per sample on one cobas e 601 analyzer, using one reagent lot for each assay. The results of the precision studies are summarized below:

Elecsys PTH					
Sample	Mean (pg/mL)	Repeatability (within-run)		Intermediate Precision (within-lab)	
		SD (pg/mL)	CV (%)	SD (pg/mL)	CV (%)
Serum 1	9.29	0.20	2.1	0.40	4.4
Serum 2	13.8	0.21	1.5	0.42	3.0
Serum 3	54.6	0.44	0.8	0.80	1.5
Serum 4	2467	17.7	0.7	32.6	1.3
Serum 5	4514	41.2	0.9	49.1	1.1
PC V0	24.5	0.29	1.2	0.54	2.2
PC V1	58.0	0.55	0.9	1.20	2.1
PC V2	175	1.60	0.9	2.56	1.5

Elecsys PTH STAT					
Sample	Mean (pg/mL)	Repeatability (within-run)		Intermediate Precision (within-lab)	
		SD (pg/mL)	CV (%)	SD (pg/mL)	CV (%)
Serum 1	9.27	0.22	2.4	0.41	4.4
Serum 2	14.0	0.24	1.7	0.39	2.8
Serum 3	54.0	0.57	1.0	0.89	1.6
Serum 4	2399	14.0	0.6	36.8	1.5
Serum 5	4390	34.9	0.8	49.0	1.1
PC V0	22.3	0.29	1.3	0.52	2.3
PC V1	49.9	0.53	1.1	1.07	2.1
PC V2	151	1.10	0.7	2.58	1.7

Reproducibility

A reproducibility study was conducted using six serum pools and three control levels. Samples were measured at three sites (one internal and two external sites). Samples with a concentration greater than 2000 pg/mL were spiked with human PTH (1-84). At the external sites, a single reagent lot was used to assay samples. At the internal site, three reagent lots were used to assay samples. At each site, samples were assayed using the cobas e 601 analyzer over five days, one run per day, 5 replicates per run. The between lot, between day, and reproducibility results are shown in the tables below:

Elecsys PTH								
Sample	N	Mean	Between Lot		Between Day		Reproducibility	
			SD (pg/mL)	CV (%)	SD (pg/mL)	CV (%)	SD (pg/mL)	CV (%)
Serum 1	125	9.62	0.075	0.78	0.22	2.27	0.59	6.09
Serum 2	125	15.1	0.13	0.88	0.20	1.35	0.57	3.76
Serum 3	125	63.2	1.06	1.68	0.54	0.85	1.44	2.28
Serum 4	125	2378	16.7	0.70	30.6	1.29	50.6	2.13
Serum 5	125	4495	24.8	0.55	55.6	1.24	84.5	1.88
Serum 6	125	4472	19.5	0.44	62.0	1.39	180	4.02
PC V0	125	27.2	0.63	2.32	0.43	1.58	0.85	3.12
PC V1	125	59.2	1.06	1.79	0.62	1.05	1.38	2.34
PC V2	125	177	2.62	1.49	2.01	1.14	3.72	2.11

Elecsys PTH STAT								
Sample	N	Mean	Between Lot		Between Day		Reproducibility	
			SD (pg/mL)	CV (%)	SD (pg/mL)	CV (%)	SD (pg/mL)	CV (%)
Serum 1	125	9.33	0.22	2.39	0.30	3.20	1.01	10.8
Serum 2	125	14.9	0.22	1.44	0.33	2.21	0.97	6.50
Serum 3	125	62.9	0	0	0.93	1.49	2.07	3.29
Serum 4	125	2366	20.7	0.88	23.5	0.10	57.4	2.43
Serum 5	125	4506	29.6	0.66	35.4	0.79	197	4.36
Serum 6	125	4463	32.1	0.72	42.6	0.95	135	3.02
PC V0	125	25.2	0.13	0.50	0.51	2.03	1.48	5.88
PC V1	125	52.0	0	0	0.48	0.92	2.25	4.33
PC V2	125	155	0	0	1.74	1.12	6.82	4.40

2. Linearity:
   A linearity study was performed in accordance with the CLSI EP06-Second Edition guideline. High and low serum sample pools were intermixed to create samples that contained human PTH with concentrations that ranged from 4.18 to 5635 pg/mL for the Elecsys PTH Immunoassay and from 3.83- 5517 pg/mL for the Elecsys PTH STAT Immunoassay. Each sample was tested in quadruplicate. Reported differences (i.e., absolute and % relative deviation from linearity) were calculated by Weight Variance (WLS). The results of the linearity study support the claimed measuring range of 6-5000 pg/mL.

3. Analytical Specificity/Interference:
   An endogenous and exogenous interference study was performed in accordance with the CLSI EP07-A3 guideline. Human serum specimen pools with native analyte were supplemented with potentially interfering compounds at levels listed in the table below. PTH analyte levels of approximately 15 pg/mL, 60 pg/mL, 2000-2500 pg/mL, and 3000-3500 pg/mL were tested. The sponsor provided information to support the following claims:

Endogenous Substances	Concentration Tested that did not interfere
Biotin	1200 ng/mL
Lipemia (Intralipid)	1500 mg/dL
Hemoglobin	100 mg/dL (PTH) 250 mg/dL (PTH STAT)
Bilirubin*	66 mg/dL
Rheumatoid Factor	1200 IU/mL
Serum Albumin	7 g/dL
Human IgG	1.4 g/dL
Human IgM	0.2 g/dL
Human IgA	0.48 g/dL
Triglyceride	2009 mg/dL

*90% unconjugated + 10% conjugated Bilirubin

Exogenous Substances	Concentration Tested that did not interfere (mg/L)
Acetylcysteine	150
Acetylsalicylic Acid	30
Ampicillin-Na	75
Ascorbic acid	52.5
Cefoxitin	750
Doxycycline	18
Heparin	3300 IU/L
Levodopa	7.5
Methyldopa	22.5
Metronidazole	123
Rifampicin	48
Acetaminophen	156
Cyclosporine	1.8
Ibuprofen	219
Theophylline	60
Phenylbutazone	321
Itraconazole	30
Fosamax	210
Cinacalcet	108
Sevelamer	2880
Calcitriol	0.00103

Cross-reactivity:
A cross-reactivity study was performed for the Elecsys PTH and Elecsys PTH STAT Immunoassays on the cobas e 601 analyzer. Cross-reactants were added at defined concentrations to native human serum samples with approximate PTH concentrations of 15 and 65 pg/mL. The acceptance criteria for cross-reactivity was ≤ 0.1% for PTH 1-34 and PTH 1-37, ≤0.1% for PTH related protein (rP) (1-86), and >50% for PTH 7-84. The % cross-reactivity was calculated for all samples using the following equation:

$$\% \text{ Cross-reactivity} = \frac{(\text{Mean Conc. Test (pg/mL)} - \text{Mean Conc. Control (pg/mL)}) \times 100}{\text{Concentration Cross-reactant (pg/mL)}}$$

Cross Reactant	Concentration Tested (pg/mL)	% Cross Reactivity
PTH (1-34)	5000	< 0.05%
PTH (1-37)	5000	< 0.07%
PTH rP (1-86)	5000	< 0.03%
PTH (7-84)	5000	96%

The following limitation statement is present in the labeling: "No cross-reactivities were found for: PTH fragment 1-34, PTH fragment 1-37 and PTH-related protein (1-86). The assay has a 96 % cross-reactivity to the PTH fragment 7-84."

Effect of HAMA:
The effect of the presence of human anti-mouse antibodies (HAMA) on the Elecsys PTH and Elecsys PTH STAT immunoassays was assessed on the cobas e 601 analyzer. Twelve native samples that were HAMA-positive and HAMA-negative were tested as shown below.

Sample	HAMA concentration (ng/mL)	Elecsys PTH		Elecsys PTH STAT	
		PTH Concentration (pg/mL)	% Recovery	PTH Concentration (pg/mL)	% Recovery
Sample 1 near MDP 1 ~15 pg/mL	0	10.2	-	10.2	-
	2.7	10.1	99%	9.87	97%
	5.4	10.3	101%	10.1	99%
	7.1	10.4	102%	10.3	101%
	11	10.6	104%	10.5	103%
	27	11.7	115%	11.5	112%
	54	12.9	127%	13.7	134%
	71	14.2	140%	14.8	145%
	107	16.6	163%	16.7	164%
	268	26.0	254%	28.4	278%
	535	40.7	399%	46.3	454%
	1070	74.1	726%	84.2	825%

Sample	HAMA concentration (ng/mL)	Elecsys PTH		Elecsys PTH STAT	
		PTH Concentration (pg/mL)	% Recovery	PTH Concentration (pg/mL)	% Recovery
Sample 2 near MDP 2 ~60 pg/mL	0	57.8	-	57.3	-
	2.7	58.0	100%	57.3	100%
	5.4	58.2	101%	57.3	100%
	7.1	57.2	99%	57.6	100%
	11	58.2	101%	58.0	101%
	27	58.5	101%	58.6	102%
	54	60.2	104%	60.9	106%
	71	61.5	106%	62.3	109%
	107	64.0	111%	64.5	113%
	268	76.8	133%	75.9	133%
	535	92.2	160%	95.1	166%
	1070	124	214%	131	228%
Sample 3 High ~2000-3000 pg/mL	0	3011	-	3028	-
	2.7	2985	99%	3016	100%
	5.4	2980	99%	3000	99%
	7.1	2986	99%	3002	99%
	11	2989	99%	2988	99%
	27	2985	99%	2994	99%
	54	2960	98%	2980	98%
	71	2972	99%	2991	99%
	107	2967	99%	3008	99%
	268	3020	100%	3033	100%
	535	3011	100%	3026	100%

The sponsor included the following limitation in their labeling:

> "For assays using antibodies, the possibility exists for interference by heterophile antibodies in the patient's sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures using immunoglobulin or immunoglobulin fragments may produce antibodies (e.g. human anti-mouse antibodies, or HAMA) that can interfere with immunoassays.
>
> The Elecsys PTH STAT assay may be affected by HAMA interference. In cases in which samples contain HAMA, a positive bias may be observed. In an internal study, the following biases were seen: for HAMA levels up to approximately 30 ng/mL, +15 % at a low PTH concentration (10 pg/mL PTH), no effect on higher PTH concentrations

(approximately 60 pg/mL and 3000 pg/mL); for HAMA levels between approximately 50-1000 ng/mL up to
8-fold increase at a low PTH concentration (10 pg/mL PTH) and 2-fold increase at a higher PTH concentration (approximately 60 pg/mL PTH). No effect was observed at approximately 3000 pg/mL PTH. Carefully evaluate the results of patients suspected of having these antibodies.

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings."

High Dose Hook Effect:
For the Elecsys PTH and Elecsys PTH STAT immunoassays, assessed on one cobas e 601 analyzer, no high dose effect was observed for samples containing approximately 17,000 pg/mL PTH.

4. Assay Reportable Range:
See section VII.A.2 Linearity.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):
Performance established in K070709 and K992680.

6. Detection Limit:
The sponsor provided detection limits studies following CLSI EP17-A2 guideline.

Limit of Blank (LoB):
The LoB was determined by testing three reagent lots on one cobas e 601 analyzer, with six runs over three days with one blank sample with ten replicates per run. The zero-level (blank) sample used was a depleted human serum sample pool and 60 measurements were analyzed. LoB was based on the determination of the 95th percentile of the 60 measured values. The claimed LoB for the Elecsys PTH immunoassay and PTH STAT immunoassay is 1.2 pg/mL.

Limit of Detection (LoD):
The LoD was determined by testing five serum samples containing low levels of PTH with three reagent lots on one cobas e 601 analyzer. Samples were run in two replicates per run, six runs over multiple days. The LoD was calculated based on LoD = LoB + 1.653 x SD (total of low analyte samples) and defined as the lowest concentration at which there is a 95% probability that a sample contains analyte. The claimed LoD for Elecsys PTH immunoassay and PTH STAT immunoassay is 2.4 pg/mL.

Limit of Quantitation (LoQ):
The LoQ for the Elecsys PTH immunoassay was determined by testing eight low level serum samples measured in five-fold determinations on one cobas e 601 analyzer with one run per day over five days using three reagent lots. The LoQ for the Elecsys PTH STAT immunoassay was determined by testing six low-level human serum samples measured in five-fold determinations on one cobas e 601 analyzer with one run per day over five days using three reagent lots. The LoQ for both immunoassays was defined as the lowest analyte concentration that can be reproducibly measured with an intermediate precision CV of ≤ 20 % and was determined to be 6 pg/mL.

7. Assay Cut-Off:
   Not applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:
   A method comparison study was performed to compare the results of the Elecsys PTH and PTH STAT immunoassays (candidate immunoassays) to the Elecsys PTH and PTH STAT immunoassays (predicate immunoassays), respectively. The samples tested ranged from 6.16 to 4751 pg/mL for the Elecsys PTH Immunoassay and 10.3- 4532 pg/mL for the Elecsys PTH STAT Immunoassay. The data analysis was conducted using weighted Deming regression analysis and results are summarized in the following tables:

Elecsys PTH Immunoassay			
n	Correlation Coefficient (r)	Intercept (95% CI)	Slope (95% CI)
257	1.000	0.272 (0.139 to 0.404)	0.968 (0.965-0.972)

Elecsys PTH STAT Immunoassay			
n	Correlation Coefficient (r)	Intercept (95% CI)	Slope (95% CI)
216	1.000	-1.228 (-1.339 to -1.117)	0.982 (0.979 to 0.986)

2. Matrix Comparison:
   A matrix comparison study was performed by testing seventy-one (71) matched sets of serum (serum separator tubes) and plasma (K2EDTA and K3 EDTA) samples. The results are presented in the following tables:

Elecsys PTH Serum vs K2-EDTA and K3-EDTA Summary:

Sample Type Comparison	Slope	Intercept	Correlation Coefficient
Serum/K2-EDTA	1.010	0.781	0.997
Serum/K3-EDTA	1.009	0.469	0.998

Elecsys PTH STAT Serum vs K2-EDTA and K3-EDTA Summary:

Sample Type Comparison	Slope	Intercept	Correlation Coefficient
Serum/K2-EDTA	1.012	0.964	0.997
Serum/K3-EDTA	1.019	0.530	0.998

The study results support the sponsor's claim that human serum and plasma (K2 EDTA, K3 EDTA and standard sampling tubes) are acceptable sample types to be used with this assay.

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):
   Performance was established in K070709.

D Clinical Cut-Off:
Not applicable

E Expected Values/Reference Range:
The reference range was assessed in accordance with CLSI EP28 using 141 serum samples collected from apparently healthy male and female donors. The 2.5th and 97.5th percentiles and corresponding intervals were computed using a nonparametric method for all sites combined.

The reference range for Elecsys PTH and Elecsys PTH STAT is 17.9-58.6 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.