510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT

I Background Information:

A 510(k) Number
K220911

B Applicant
Roche Diagnostics

C Proprietary and Established Names
Elecsys CMV IgG

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
LFZ	Class II	21 CFR 866.3175 - Cytomegalovirus Serological Reagents	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:
Clearance of modifications to the Elecsys CMV IgG assay that improve tolerance to biotin interference.

B Measurand:
IgG antibodies to Cytomegalovirus (CMV)

C Type of Test:
Electrochemiluminescence immunoassay (ECLIA)

III Intended Use/Indications for Use:

A Intended Use(s):
The Elecsys CMV IgG assay is an in vitro qualitative test for the detection of IgG antibodies to CMV in human serum, lithium-heparin plasma, K2-EDTA plasma, and K3-EDTA plasma. The

test is intended as an aid in the determination of the serological status to CMV in individuals in which a CMV IgG test was ordered, including pregnant women.

Performance characteristics have not been evaluated in immunocompromised or immunosuppressed individuals. This test is not intended for use in neonatal screening or for use at point of care facilities. This test is not intended for use in screening blood and plasma donors.

The electrochemiluminescence immunoassay "ECLIA" is intended for use on cobas e immunoassay analyzers.

B Indication(s) for Use:
See intended use above.

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

D Special Instrument Requirements:
The electrochemiluminescence immunoassay "ECLIA" is intended for use on cobas e immunoassay analyzers.

IV Device/System Characteristics:

A Device Description:
The Elecsys CMV IgG assay is a two-step sandwich immunoassay with streptavidin microparticles, biotinylated recombinant CMV-specific antigen labeled with a ruthenium complex and electrochemiluminescence detection. The results are determined using a calibration curve which is instrument-specifically generated by a 2-point calibration and a master curve provided via the reagent bar code. Results greater than or equal to 1.0 COI are considered reactive CMV IgG antibody. The test system contains the human serum-based calibrators intended for use with the system.

The Elecsys PreciControl CMV IgG contains liquid control serum based on human serum. The controls are used for monitoring the accuracy of the Elecsys CMV IgG immunoassay.

Reagents and calibrators are packaged together in the Elecsys CMV IgG assay kit, while the associated PreciControl is packaged separately.

The following Reagents are provided in the Elecsys CMV IgG assay kit:

1. The reagent rackpack consists of reagents: M, R1, and R2 and is labeled as CMVIGG:
   - M: Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL: Streptavidin-coated microparticles 0.72 mg/mL; preservatives: MIT (0.1%) and Oxypyrion (0.1%).

- R1: CMV Ag~biotin (gray cap), 1 bottle, 9 mL: Biotinylated CMV-specific antigen (recombinant, E. coli) > 400 µg/L, MES buffer 50 mmol/L, pH 6.5; preservatives: MIT (1%) and Oxypyrion (1%).
- R2: CMV Ag~Ru(bpy) (black cap), 1 bottle, 9 mL: CMV specific antigen (recombinant, E. coli) labeled with ruthenium complex > 400 µg/L; MES buffer 50 mmol/L, pH 6.5; preservatives: MIT (1%) and Oxypyrion (1%).

2. CMVIGG Cal1: Negative calibrator 1 (white cap), 2 bottles of 1.0 mL each: Human serum, non-reactive for anti-CMV IgG; buffer; preservatives: MIT (0.1%) and Oxypyrion (0.1%).
3. CMVIGG Cal2: Positive calibrator 2 (black cap), 2 bottles of 1.0 mL each: Human serum, reactive for anti-CMV IgG, approx. 40 COI; buffer; preservatives: MIT (0.1%) and Oxypyrion (0.1%).

The following are the Materials that are required but not provided:

1. PreciControl CMV IgG, 5 x 1 mL each of PreciControl CMV IgG 0, 1 and 2
2. 11776576322, CalSet Vials, 2 x 56 empty snap-cap bottles
3. General laboratory equipment
4. Elecsys 2010, MODULAR ANALYTICS E170 or cobas e analyzer
5. Accessories for cobas e immunoassay analyzer

Calculation

The analyzer automatically calculates the analyte numerical value of each sample in COI.

Interpretation of Results

Interpretation of the results is tabulated below:

Numerical Value COI	Result	Interpretation
< 0.5 COI	Non-reactive	CMV IgG antibodies not detected
0.5 - < 1.0 COI	Borderline	Re-test the sample, collect another sample within 2 weeks or test with an alternative method
≥ 1.0 COI	Reactive	CMV IgG antibodies detected

B Principle of Operation:

Sandwich principle. Total duration of assay: 18 minutes.

- *1st incubation*: 12 µL of sample, biotinylated recombinant CMV-specific antigens, and CMV-specific recombinant antigens labeled with a ruthenium complex[a)] form a sandwich complex.
- *2nd incubation*: After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.

- The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell II M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined via a calibration curve which is instrument specifically generated by 2-point calibration and a master curve provided via the cobas link.

[a] - Tris(2,2'-bipyridyl)ruthenium(II)-complex (Ru(bpy))

C Instrument Description Information:

1. Instrument Name:
   cobas e 801 analyzer

2. Specimen Identification:
   See K131605.

3. Specimen Sampling and Handling:
   See K131605.

4. Calibration:
   See K131605.

5. Quality Control:
   See K131605.

V Substantial Equivalence Information:

A Predicate Device Name(s):
Elecsys Precicontrol CMV IgG, Elecsys CMV IgG Immunoassay

B Predicate 510(k) Number(s):
K131605

C Comparison with Predicate(s):

Table 1: Comparison of the Biotin-Updated Elecsys CMV IgG (K220911) with the Predicate (K131605)

Device & Predicate Device(s):	K220911	K131605
Device Trade Name	Elecsys CMV IgG	Elecsys CMV IgG
Catalog number	09118551190 (300 test kit)	07027117190 (300 test kit)
General Device Characteristic Similarities		
Intended Use/Indications For Use	The Elecsys CMV IgG assay is an in vitro qualitative test for the detection of IgG antibodies to CMV in human serum, lithium-heparin plasma, K2- EDTA plasma, and K3-EDTA plasma. The test is intended as an aid in the determination of the serological status to CMV in individuals in which a CMV IgG test was ordered, including pregnant women. Performance characteristics have not been evaluated in immunocompromised or immunosuppressed individuals. This test is not intended for use in neonatal screening or for use at point of care facilities. This test is not intended for use in screening blood and plasma donors. The electrochemiluminescence immunoassay "ECLIA" is intended for use on cobas e immunoassay analyzers.[1]	The Elecsys CMV IgG assay is an in vitro qualitative test for the detection of IgG antibodies to CMV in human serum, lithium-heparin plasma, K2- EDTA plasma, and K3-EDTA plasma. The test is intended as an aid in the determination of the serological status to CMV in individuals in which a CMV IgG test was ordered, including pregnant women. Performance characteristics have not been evaluated in immunocompromised or immunosuppressed individuals. This test is not intended for use in neonatal screening or for use at point of care facilities. This test is not intended for use in screening blood and plasma donors. The electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys and cobas e immunoassay analyzers.
Technology	Same	ECLIA

Test Format	Same	Sandwich
Test Type	Same	Qualitative
Application Time	Same	18 min
Assay Protocol	Same	1st Incubation: R1+R2+sample 2nd incubation: Addition of streptavidin-coated microparticles (beads)
Pipetting Volume (sample)	Same	12 µL
Pipetting Volume (beads)	Same	24 µL
Pipetting volume (R1)	Same	42 µL
Pipetting volume (R2)	Same	42 µL
Buffer Composition R1	Same	2-morpholino-ethane sulfonic acid
	Same	Preservatives: N-Methylisothiazolone Oxy-PYRION
Antigens used in R1	Same	Biotinylated CMV-specific antigen (recombinant, *E. coli*)
Buffer Composition R2	Same	2-morpholino-ethane sulfonic acid
	Same	Preservatives
Result Reporting	Same	COI and result message as defined below: (non- reactive, borderline, or reactive) < 0.5 COI = non-reactive 0.5 - <1.0 COI = borderline ≥ 1.0 COI = reactive
Calibrators	Same	CMV IgG Cal1/Cal2
Control Material	Same	PreciControl CMV IgG
General Device Characteristic Differences		
Antigens used in R2	CMV-specific antigen (recombinant, *E.coli*) labelled with ruthenium complex SA recombinant inactive poly + SA rec. Mutein poly which, increases the anti-streptavidin tolerance.	CMV-specific antigen (recombinant, *E. coli*) labeled with ruthenium complex

Antibodies used in R2	Anti-Biotin antibody ("scavenger antibody") specific for free, unconjugated biotin	None
Biotin Tolerance	≤ 1200 ng/mL	≤ 100 ng/mL
Anti-SA interference elimination	Yes	No

[1] The Elecsys instruments were discontinued and are therefore no longer included in the Intended Use.

VI Standards/Guidance Documents Referenced:

Standard/Guidance Documents referenced are below:

- Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline - Third Edition CLSI EP05-A3 7-251
- Interference Testing in Clinical Chemistry CLSI EP07 3rd Edition 7-275
- Interference Testing in Clinical Chemistry CLSI EP37 1st Edition 7-284
- User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline - Second Edition. CLSI EP12-A2 7 – 152

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Within laboratory precision was determined using Elecsys CMV IgG Immunoassay reagents, and calibrators in a protocol based on CLSI (Clinical and Laboratory Standards Institute) EP05-A3. The test panel consisted of 5 human serum samples of different CMV IgG concentrations (see Table 2) and the PreciControls. Samples and assay controls were measured in duplicates in each of 2 runs per day, for 21 days (n = 84). The following results were obtained:

Table 2: Precision of the Biotin-Updated Elecsys CMV IgG Assay

Sample	Mean [COI]	Repeatability (within-run)		Intermediate Precision (within-lab)	
		SD [COI]	CV (%)	SD [COI]	CV (%)
HS 1	0.283	0.00595	2.1	0.00788	2.8
HS 2	0.963	0.0218	2.3	0.0289	3.0
HS 3	1.08	0.0217	2.0	0.0258	2.4
HS 4	12.5	0.216	1.7	0.299	2.4
HS 5	405	3.87	1.0	7.66	1.9
PreciControl CMV IgG 0	0.132	0.00514	3.9	0.00601	4.6
PreciControl CMV IgG 1	1.32	0.0127	1.0	0.0227	1.7

PreciControl CMV IgG 2	24.1	0.207	0.9	0.412	1.7

HS = human serum
UCL = Upper Confidence Limit

2. Linearity:
   Not applicable since this is not a quantitative assay.

3. Analytical Specificity/Interference:
   To evaluate the effect of elevated levels of hemoglobin, bilirubin, intralipid, total protein and rheumatoid factor on the CMV IgG assay, six CMV IgG samples (2 negative, 2 near cutoff and 2 positive) were spiked with the potential interferents. Each interferent was evaluated at 11 different concentrations. Samples containing hemoglobin, bilirubin, intralipid, total protein, and rheumatoid factor were tested in duplicate on the Elecsys 2010 analyzer with an acceptance criterion of ± 15 % Please refer to the interfering substances testing in K131605.

   Biotin interference testing was performed with multiple samples of increasing biotin concentrations using an acceptance criterion of ± 10 %.

   The results of the biotin interference testing are presented in the following table with the maximum test concentration that does not interfere with the results of the Elecsys CMV IgG test:

Table 3: Endogenous Interfering Substances Testing

Interferent tested	No interference up to
Hemoglobin	≤ 0.623 mmol/L or ≤ 1.0 g/dL
Bilirubin	≤ 1129 µmol/L or ≤ 66 mg/dL
Intralipid	≤ 2000 mg/dL
Biotin	≤ 4912 nmol/L or ≤ 1200 ng/mL
Total protein	≤ 20 g/dL
Rheumatoid factor	≤ 1600 IU/mL

4. Assay Reportable Range:
   See K131605.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):
   a. *Traceability:*
      See K131605.

b. *Reagent Stability*:
Roche conducted the following reagent stability studies to determine changes to the stability of the biotin updated Elecsys CMV IgG assay:

- *On board Reagent Stability*: The on-board stability of the reagents were assessed in this study with one lot on the cobas e 801 analyzer. The study was conducted with a panel that consisted of five human serum samples (negative, below cut-off, borderline, above cut-off, positive) and PreciControl PC0, PC1 and PC2. Each panel member was tested in duplicates. Samples were measured with reagent kits of one lot on day 0 (reference value with fresh reagents), and upon storage of the reagent kit at 10 °C +/- 2°C onboard of the instrument for 35, 63, 91, 112 and 119 days (5, 9, 13, 16 and 17 weeks). Re-calibration was performed at every measuring time point. The study results met the following criteria and thus supports a claim of 16 weeks at on-board temperature of 10 °C +/- 2°C:

Concentration	**Deviation/Recovery**
0.25 COI to ≤ 1.0 COI	± 0.2 COI
> 1.0 COI	≤ ± 20 %

- *Calibration Stability*: The calibration stability of the reagents were assessed in this study with one lot of calibrators on the cobas e 801 analyzer. The study was conducted with a panel that consisted of five human serum samples (negative, below cut-off, borderline, above cut-off, positive) and PreciControl PC0, PC1 and PC2. Each panel member was tested in duplicates at each timepoint. Samples were tested at day 0 (reference value with new reagents, stored refrigerated at 2-8°C) and then assessed for their stability at day 35, 63, 84 and 91 of open reagents stored at 2-8°C during the entire test period. The median sample COI was calculated and evaluated on the basis of recovery (absolute or percentage) relative to the median of the test samples with fresh reagents (reference). The study results met the following criteria and thus supports a calibration stability claim for 12 weeks when stored at 2-8°C:

Concentration	**Deviation/Recovery**
0.25 COI to ≤ 1.0 COI	± 0.15 COI
> 1.0 COI	≤ ± 15 %

c. *Expected Values:*
See K131605.

6. Detection Limit:
Not applicable.

7. Assay Cut-Off:
   See K131605.

8. Accuracy (Instrument):
   See K131605.

9. Carry-Over:
   See K131605.

B Comparison Studies:

1. Method Comparison with Predicate Device:
   The equivalence of the current and biotin-updated Elecsys CMV IgG assay was evaluated by a method comparison study. A total of 280 samples were measured with one lot of the current Elecsys CMV IgG assay and 3 lots of the biotin-updated Elecsys CMV IgG assay. Testing was conducted with the cobas e 801 analyzer at one site.

   Native clinical and contrived samples were tested in this study to adequately represent the measuring range of the Elecsys CMV IgG assay. Contrived samples were derived from diluting individual positive samples with individual negative clinical samples for concentrations that were not adequately represented by native clinical samples. Sample concentrations were as follows:
   - 80 samples - < 0.5 COI,
   - 31 samples were between 0.5 to < 1.0 COI
   - 69 samples were between 1.0 – 3.0 COI
   - 100 samples were > 3.0 COI

   The results are presented below:

Table 4: Method Comparison Study: Current (Lot 522583) vs. Updated (Lots 546722, 546723, and 546724) Elecsys CMV IgG Assay

Interpretation of Gray Zone Samples	Percent Positive Agreement	95.0 % Confidence Limits		Percent Negative Agreement	95.0 % Confidence Limits	
		LCL	UCL		LCL	UCL
Biotin Updated Elecsys CMV IgG (Lot 546722)						
All gray + (Borderlines counted as pos)	99.0 %	96.4 %	99.9 %	100.0 %	95.5 %	100.0 %
All gray - (Borderlines counted as neg)	99.4 %	96.7 %	100.0 %	99.1 %	95.1 %	100.0 %
Conservative Approach[1]	98.2 %	95.0 %	99.6 %	98.8 %	93.3 %	100.0 %

Biotin-Updated Elecsys CMV IgG (Lot 546723)						
All gray + (Borderlines counted as pos)	99.5 %	97.2 %	100.0 %	100.0 %	95.5 %	100.0 %
All gray – (Borderlines counted as neg)	97.0 %	93.2 %	99.0 %	100.0 %	96.7 %	100.0 %
Conservative Approach[1]	96.5 %	92.5 %	98.7 %	100.0 %	95.5 %	100.0 %
Biotin-Updated Elecsys CMV IgG (Lot 546724)						
All gray + (Borderlines counted as pos)	100.0 %	98.2 %	100.0 %	100.0 %	95.5 %	100.0 %
All gray - (Borderlines counted as neg)	98.8 %	95.8 %	99.9 %	100.0 %	96.7 %	100.0 %
Conservative Approach[1]	98.8 %	95.8 %	99.9 %	100.0 %	95.5 %	100.0 %

[1] – the conservative approach counts the equivocals of the candidate and comparator assay against the candidate device

The results presented above support the equivlance of the current Elecsys CMV IgG and the biotin-updated Elecsys CMV IgG assays.

2. Matrix Comparison:
   See K131605.

C Clinical Studies:

1. Clinical Sensitivity:
   See K131605.

2. Clinical Specificity:
   See K131605.

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:
See K131605.

F Other Supportive Instrument Performance Characteristics Data:
Not applicable.

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.