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

## I Background Information:

### A 510(k) Number

K260233

### B Applicant

Roche Diagnostics

### C Proprietary and Established Names

Elecsys EBV IgM

### D Regulatory Information

| Product Code(s) | Classification | Regulation Section | Panel |
|---|---|---|---|
| LJN | Class I | 866.3235 Epstein-Barr virus serological reagents | Microbiology |

## II Submission/Device Overview:

### A Purpose for Submission:

To obtain clearance of a new device

### B Measurand:

Epstein Barr Virus IgM antibody (EBV IgM)

### C Type of Test:

The Elecsys EBV IgM assay is a fully automated, qualitative, chemiluminescent immunoassay (CLIA)

## III Intended Use/Indications for Use:

See Indications for Use below.

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

**B Indication(s) for Use:**

Immunoassay for the in vitro qualitative detection of IgM antibodies to Epstein-Barr virus in human serum and plasma. When performed in conjunction with other Epstein-Barr virus markers, this assay is intended for use as an aid in the diagnosis of Epstein-Barr virus infection, such as infectious mononucleosis.
The electrochemiluminescence immunoassay "ECLIA" is intended for use on cobas e immunoassay analyzers.

**C Special Conditions for Use Statement(s):**

Rx - Prescription use only

**D Special Instrument Requirements:**

cobas e 801 analyzer

## IV Device/System Characteristics:

**A Device Description:**

The Elecsys EBV IgM test is an electrochemiluminescence immunoassay (ECLIA) to detect IgM antibodies to EBV.

Elecsys EBV IgM kit is comprised of a **cobas** e pack, and EBV IgM CalSet

**cobas e pack:**
cobas e pack has the following components:

- R1 contains biotinylated monoclonal mouse anti-human-IgM antibody fragments
- R2 contains EBV-specific antigens (recombinant, E. coli) labeled with ruthenium complex
- M contains streptavidin-coated microparticles

EBV IgM Calibrators (EBV IgM CalSet):
The Elecsys EBV IgM assay is calibrated using EBV IgM calibrators. The calibrator materials are in lyophilized human serum matrices.

Two levels of calibrators are provided:
1. Negative calibrator 1
2. Positive calibrator 2

Material required but not part of the cobas e pack components

**PreciControl EBV IgM/VCA IgG:**

PreciControls are used to verify the performance of the Elecsys EBV IgM assay on the cobas e 801 analyzer. There are 2 levels of control material provided:
1. Negative control, EBV IgM Level 1
2. Positive control, EBV IgM Level 2

The control kit is packaged and sold separately

## B Principle of Operation:

The Elecsys EBV IgM is a qualitative, serological, sandwich immunoassay to be used on the **cobas** e 801 immunoassay analyzer with an overall 18-minute test time.

There are two incubation steps in the assay. First incubation: 6 µL of sample are automatically prediluted 1:20 with Diluent Universal. Biotinylated monoclonal anti-human IgM-specific antibody fragments are added.

Second incubation: EBV-specific recombinant antigens a) labeled with a ruthenium complex b) and streptavidin-coated microparticles are added. Anti-EBV IgM antibodies present in the sample react with the ruthenium-labeled EBV-specific recombinant antigens. 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 automatically by the software by comparing the electrochemiluminescence signal obtained from the reaction product of the sample, with the signal of the cutoff value previously obtained by calibration.

**Interpretation of the results**:

The analyzer automatically calculates the cutoff based on the measurement of EBVIGM Cal1 and EBVIGM Cal2. The result of a sample is given either as reactive or non-reactive as well as in the form of a cutoff index (COI; signal sample/cutoff).
Results obtained with the Elecsys EBV IgM assay can be interpreted as follows:

| Numeric result | Qualitative Result | Interpretation |
|---|---|---|
| COI < 1.0 | Non-reactive | Negative for EBV-specific IgM |
| COI ≥ 1.0 | Reactive | Positive for EBV-specific IgM |

The magnitude of the measured result above the cutoff is not indicative of the total amount of antibody present in the sample.

## C Instrument Description Information:

1. Instrument Name:

   cobas e 801 analyzer

2. Specimen Identification:

   Specimen identification can be done by a bar code scanning method.

3. Specimen Sampling and Handling:

   The cobas e 801analyzer handles samples through an automated rack-based system, supporting continuous loading/unloading of up to 300 samples for high-throughput immunoassays.

4. Calibration:

   Calibration must be performed as:

- once per reagent lot using EBVIGM Cal1, EBVIGM Cal2 and fresh reagent

   Renewed calibration is recommended as follows:

- every 12 weeks when using the same reagent lot
- every 28 days when using the same cobas e pack on the analyzer
- as required, such as when quality control findings are outside the defined limits

5. Quality Control:

   For quality control, the Elecsys EBV IgM assay uses PreciControl EBV IgM/VCA IgG QC is run:

- every 24 hours when test is in use
- once per cobas e-pack
- following each calibration

  The control values should be within the expected control interval for the system.

## V Substantial Equivalence Information:

### A Predicate Device Name(s):

LIAISON EBV IgM

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

K040120

## C Comparison with Predicate(s):

| Device & Predicate Device(s): | K040120 (Predicate device) | K260233 (Candidate device) |
|---|---|---|
| Device Trade Name | LIAISON EBV IgM | Elecsys EBV IgM |
| **General Device Characteristic Similarities** | | |
| Intended Use/Indications For Use | The LIAISON EBV IgM assay uses chemiluminescent immunoassay (CLIA) technology on the LIAISON Analyzer family for the qualitative determination of specific IgM antibodies to Epstein-Barr virus (EBV) viral capsid antigen (VCA) p18 synthetic peptide in human serum. When performed in conjunction with other EBV markers, this assay can be used as an aid in the clinical laboratory diagnosis of Epstein-Barr Viral Syndrome in patients with signs and symptoms of EBV infection such as infectious mononucleosis.<br><br>Caution: U.S. Federal Law restricts this device to sale by or on the order of a licensed practitioner. | Immunoassay for the in vitro qualitative detection of IgM antibodies to Epstein-Barr virus in human serum and plasma. When performed in conjunction with other Epstein-Barr virus markers, this assay is intended for use as an aid in the diagnosis of Epstein-Barr virus infection, such as infectious mononucleosis.<br><br>The electrochemiluminescence immunoassay "ECLIA" is intended for use on cobas e immunoassay analyzers. |
| Assay Type | Qualitative | Same |
| Technology | Electrochemiluminescence immunoassay | Same |
| **General Device Characteristic Differences** | | |
| Measurand | EBV VCA IgM | EBV IgM |
| Sample matrix | Serum | Serum<br>Li-heparin plasma,<br>K2-EDTA plasma,<br>K3-EDTA plasma |
| Results interpretation | < 36 U/mL - Negative<br>36.0 – 43.9 U/mL - Equivocal<br>≥ 44.0 U/mL - Positive | COI < 1.0- Non-reactive<br>COI ≥ 1.0 - Reactive |
| Calibrator | Human serum/defibrinated plasma containing low EBV IgM levels<br>Human serum/defibrinated plasma containing high EBV IgM levels | Human serum, negative calibrator<br><br>Human serum, positive calibrator |
| Instrument Platform | LIAISON Analyzer, LIAISON XL Analyzer | **cobas** e analytical unit |
| Applications/Test Time | 30 minutes - LIAISON Analyzer<br>15 minutes - LIAISON XL Analyzer | 18 minutes on cobas e analyzer |
| | Previous calibration more than 2 weeks before | Every 12 weeks using same lot |

| | | |
|---|---|---|
| | Analyzer service<br>QC outside of expected ranges | Every 28 days using same kit<br>As required if QC outside of defined limits |

## VI Standards/Guidance Documents Referenced:

1. EP05-A03: Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline - Third Edition
2. EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline
3. EP07-3rd: Interference Testing in Clinical Chemistry - Third Edition
4. EP37: Supplemental Tables for Interference Testing in Clinical Chemistry – First Edition

## VII Performance Characteristics (if/when applicable):

### A Analytical Performance:

1. Precision/Reproducibility:

#### A. Within-Laboratory Precision study:

A precision study was conducted to establish within-laboratory precision of the Elecsys EBV IgM on the cobas e 801 analyzer. Five plasma samples covering the analytical range and two controls were tested at one run per day, four replicates per run, with one reagent lot for twenty-one days. Table 1 shows the within-laboratory precision results.

**Table 1. Within laboratory precision results for the Elecsys EBV IgM on the cobas e 801 analyzer**

| Sample | N | Mean COI | Repeatability | | Between-run/day | | Intermediate precision (Within-laboratory) | |
|---|---|---|---|---|---|---|---|---|
| | | | SD COI | CV % | SD COI | CV % | SD COI | CV % |
| Sample 1 | 84 | 0.004 | 0.021 | 541 | 0.013 | 320 | 0.025 | 6.29 |
| Sample 2 | 84 | 1.51 | 0.034 | 2.26 | 0.029 | 1.91 | 0.045 | 2.96 |
| Sample 3 | 84 | 1.80 | 0.037 | 2.05 | 0.027 | 1.52 | 0.046 | 2.55 |
| Sample 4 | 84 | 2.26 | 0.046 | 2.05 | 0.035 | 1.54 | 0.058 | 2.56 |
| Sample 5 | 84 | 20.5 | 0.389 | 1.90 | 0.281 | 1.37 | 0.480 | 2.35 |
| PC1 EBV-MG1 | 84 | 0.120 | 0.021 | 17.1 | 0.012 | 9.88 | 0.024 | 19.7 |
| PC2 EBV-MG2 | 84 | 4.92 | 0.064 | 1.30 | 0.070 | 1.42 | 0.095 | 1.93 |

N= Number of replicates, PC= Plasma controls

A study was conducted to demonstrate lot-to-lot variability between the Elecsys EBV IgM assay on the cobas e 801 analyzer. Five plasma samples and two controls were run with 3

reagent lots at 5 replicates per run, one run per day for 5 days on one cobas e 801 analyzer. The results of the between lot precision study are presented in table 2.

**Table 2. Between lot precision of the Elecsys EBV IgM on the cobas e 801 analyzer**

| Sample | Mean COI | N | Repeatability | | Between-Day/run | | Between-Lot | | Within-Laboratory (total) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | SD | CV (%) | SD | CV (%) | SD | CV (%) | SD | CV (%) |
| Sample 1 | 0.065 | 75 | 0.015 | 23.2 | 0.009 | 14.5 | 0.026 | 39.1 | 0.031 | 47.7 |
| Sample 2 | 0.563 | 75 | 0.013 | 2.3 | 0.024 | 4.3 | 0.061 | 10.9 | 0.067 | 11.9 |
| Sample 3 | 2.12 | 75 | 0.031 | 1.4 | 0.120 | 5.7 | 0.186 | 8.8 | 0.224 | 10.6 |
| Sample 4 | 1.11 | 75 | 0.023 | 2.1 | 0.051 | 4.6 | 0.091 | 8.2 | 0.107 | 9.6 |
| Sample 5 | 8.42 | 75 | 0.137 | 1.6 | 0.283 | 3.4 | 0.720 | 8.6 | 0.786 | 9.3 |
| PC1 EBV IgM | 0.210 | 75 | 0.013 | 6.2 | 0.017 | 8.1 | 0.037 | 17.5 | 0.043 | 20.2 |
| PC2 EBV IgM | 5.27 | 75 | 0.077 | 1.5 | 0.199 | 3.8 | 0.403 | 7.7 | 0.456 | 8.7 |

N= Number of replicates, PC= Preci controls

**B. Reproducibility study:**

A study was conducted to demonstrate reproducibility of the Elecsys EBV IgM assay on the cobas e 801 analyzer. In this study, 5 samples and 2 controls were tested at 2 runs per day, 3 replicates per run for 5 days with one reagent lot at 3 sites. Reproducibility results are presented on table 3.

**Table 3. Reproducibility study of the Elecsys EBV IgM on the cobas e 801 analyzer**

| Level | N | Mean COI | Repeatability | | Between-Run | | Between-Day | | Between-Sites | | Reproducibility | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | SD | %CV | SD | %CV | SD | %CV | SD | %CV | SD | %CV |
| Sample 1 | 90 | 0.100 | 0.011 | 10.5 | 0.005 | 5.08 | 0.005 | 5.30 | 0.006 | 6.44 | 0.014 | 14.4 |
| Sample 2 | 90 | 0.780 | 0.015 | 1.93 | 0.014 | 1.78 | 0.000 | 0 | 0.014 | 1.77 | 0.025 | 3.17 |
| Sample 3 | 90 | 1.25 | 0.021 | 1.72 | 0.007 | 0.599 | 0.017 | 1.40 | 0.041 | 3.32 | 0.050 | 4.04 |
| Sample 4 | 90 | 4.37 | 0.056 | 1.28 | 0.038 | 0.865 | 0.036 | 0.817 | 0.129 | 2.94 | 0.150 | 3.42 |
| Sample 5 | 90 | 8.81 | 0.148 | 1.68 | 0.073 | 0.833 | 0.074 | 0.836 | 0.325 | 3.69 | 0.372 | 4.23 |
| PC1 EBV IgM | 90 | 0.110 | 0.014 | 12.5 | 0.000 | 0 | 0.006 | 5.37 | 0.005 | 4.48 | 0.016 | 14.3 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PC2 EBV IgM | 90 | 4.50 | 0.051 | 1.13 | 0.016 | 0.346 | 0.029 | 0.650 | 0.169 | 3.76 | 0.179 | 3.99 |

N= Number of replicates, PC= Preci controls

2. Linearity:

Not applicable as the device is a qualitative assay.

3. Analytical Specificity/Interference:

**A. Cross reactivity**:

Potential cross-reactivity with the Elecsys EBV IgM assay was determined by testing specimens with antibodies to other microorganisms or with medical conditions unrelated to EBV infections. No cross reactivity was observed for the tested cross reactants. The cross-reactants tested, and study results are summarized in table 4.

**Table 4. Cross reactivity results on the Elecsys EBV IgM**

| Cross-reactants | | Elecsys EBV lgM | |
|---|---|---|---|
| | Number of samples tested | Number of reactive | Number of non-reactive |
| ANA | 11 | 0 | 11 |
| *Borrelia burgdorferi lgM | 14 | 2 | 12 |
| *CMV lgM | 18 | 4 | 14 |
| HAMA | 10 | 0 | 10 |
| HAV | 10 | 0 | 10 |
| HBc lgM | 5 | 0 | 5 |
| HCV | 5 | 0 | 5 |
| HEV lgM | 6 | 0 | 6 |
| HHV-6 lgM | 15 | 1 | 14 |
| HIV | 5 | 0 | 5 |
| HSV-1 lgM | 8 | 0 | 8 |
| *HSV-2 lgM | 5 | 1 | 4 |
| Measles lgM | 5 | 0 | 5 |
| Mumps lgM | 6 | 0 | 6 |
| Mycoplasma pneumoniae lgM | 5 | 0 | 5 |
| *Parvovirus B19 lgM | 23 | 3 | 20 |
| Rheumatoid factor | 15 | 0 | 15 |
| Rubella lgM | 12 | 0 | 12 |
| SLE/dsDNA | 10 | 0 | 10 |
| Toxoplasmosis lgM | 8 | 0 | 8 |
| Treponema pallidum lgM | 6 | 0 | 6 |
| VZV lgM | 5 | 0 | 5 |
| EBV EBNA lgG | 5 | 0 | 5 |

*Cross reactivity of the Elecsys EBV IgM against Borrelia burgdorferi IgM, CMV IgM, HHV-6 IgM, HSV-2 IgM and Parvovirus B12 IgM cannot be excluded

**B. Interference testing:**

Interference study was conducted to evaluate the susceptibility of the Elecsys EBV IgM assay to potentially interfering substances using negative, low positive, and high positive samples. Potential endogenous, and exogenous interferents were tested. No interference was observed for any of the interferents tested at concentrations indicated in tables 5 and 6.

**Table 5. Endogenous interferents tested and their concentrations on the Elecsys EBV IgM**

| Interferent Substance | Concentration |
|---|---|
| Hemoglobin | 1000 mg/dL |
| Intralipid (lipemia) | 2000 mg/dL |
| Bilirubin | 66 mg/dL |
| Biotin | 1200 ng/mL |
| Human Serum Albumin | 7 g/dL |
| Cholesterol | 400 mg/dL |

**Table 6. Exogenous interferents tested on the Elecsys EBV IgM**

| Active agent | Drug Concentration [mg/L] |
|---|---|
| N-Acetylcysteine | 150 |
| Acetylsalicylic acid | 30 |
| Ampicillin-NA | 75 |
| Ascorbic acid | 52.5 |
| Cefoxitin | 750 |
| Doxycycline | 18 |
| Heparin | 3300 IU/mL |
| Levodopa | 7.5 |
| Methyldopa +1.5 | 22.5 |
| Metronidazole | 123 |
| Rifampicin | 48 |
| Acetaminophen | 156 |
| Cyclosporine | 1.8 |
| Ibuprofen | 219 |
| Theophylline | 60 |
| Phenylbutazone | 321 |
| Itraconazol | 30 |

**C. IgM class specificity**:

A study was conducted to demonstrate that the Elecsys EBV IgM assay specifically detects IgM not IgG and does not generate false results in the presence of IgG in patients' samples. The IgM class specificity study was evaluated by depleting EBV IgM with DTT treatment. The results showed decreased signal with DTT treatment compared to untreated specimens demonstrating that the Elecsys EBV IgM assay detects IgM antibodies.

**D. Hook effect:**

A study was conducted to characterize the performance of the Elecsys EBV IgM assay with specimens containing high levels of EBV IgM that have the potential to cause a high dose hook effect. The data demonstrated that the Elecsys EBV IgM assay is not susceptible to interference from specimens with high levels EBV IgM.

4. Detection Limit (LoD):

Not applicable

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

**A. Sample stability Study**:

A sample stability study was conducted using serum, lithium heparin plasma, K2-EDTA plasma and K3-EDTA plasma to evaluate effect of temperature and storage, at room temperature (20-25ºC), refrigerated (2-8ºC) and frozen (15-25ºC) conditions. In addition, a sample freeze thaw study was performed to establish number of freeze thaw claims. Table 7 presents sample stability study results with the Elecsys EBV IgM on the cobas e 801 analyzer.

**Table 7. Sample stability results on the Elecsys EBV IgM assay on the cobas e 801 analyzer**

| Matrices | Claims at each conditions | | | |
|---|---|---|---|---|
| | 2 to 8ºC | +20 to + 25ºC | -15 to -20ºC | Freeze/thaw |
| Serum | 14 Days | 5 days | 3 months | Up to 3 times |
| Lithium Heparin plasma | | | | |
| K2-EDTA plasma | | | | |
| K3-EDTA plasma | | | | |

**B. Fresh versus frozen sample stability study:**

This study evaluated equivalency between fresh (never frozen) serum samples and samples frozen at ≤ -18°C using the Elecsys EBV IgM assay on the cobas e 801 analyzer. Total of fifty samples covering low negative, high negative, around the cut-off, and moderate positives were tested before and after freezing at -20ºC with the Elecsys EBV IgM assay on the cobas e 801 analyzer. The results demonstrated that the EBV IgM levels were comparable between fresh and frozen samples.

**C. Reagents stability study:**

On-board reagent stability:
Five samples covering negative, around the cut-off, moderately positive and high positive were tested with the EBV IgM assay on the cobas e 801 analyzer. The results showed that reagent pack at on-board conditions was stable up to 17 weeks.

Calibration stability:
Five samples covering negative, around the cut-off, moderately positive and high positives were tested with the EBV IgM test on cobas e 801 analyzer. The following stability results were obtained:
Lot calibration - up to 12 weeks
Calibration when the same cobas e pack on the analyzer – up to 28 days

6. Assay Cut-Off:

Assay cut-off of the Elecsys EBV IgM assay was evaluated testing 100 EBV IgM negative and 150 EBV IgM reactive specimens from intended use population. The results of this study established the cut-off value of 1.00 COI for the Elecsys EBV IgM assay.

## B Comparison Studies:

1. Method Comparison with Predicate Device:

Not applicable, see clinical study section C

2. Matrix Comparison:

This study was conducted to determine whether the claimed matrices have equivalent performance on the Elecsys EBV IgM assay. The study evaluated 54 sets of matched specimens collected in serum separator tube, K2 and K3 EDTA plasma, and lithium heparin plasma. Serum (without gel) served as the primary matrix type. Regression analysis showed equivalency between primary matrix and candidate matrix. The data supporting the matrix equivalence is presented in table 8.

**Table 8. Matrix comparison results of the Elecsys EBV IgM assay on the cobas e 801 analyzer**

| **Matrix equivalence results with serum as a primary matrix** | | | |
|---|---|---|---|
| **Regression parameter** | Li-Heparin plasma | K2-EDTA plasma | K3-EDTA plasma |
| **Number of samples tested** | 54 | 54 | 54 |
| **Slope (Passing-Bablok)** | 0.986 | 1.012 | 1.046 |
| **Intercept (Passing-Bablok)** | 0.00 | 0.00 | 0.00 |
| **Range tested (COI)** | 0.023 – 15.1 COI | 0.001 – 15.5 COI | 0.001 – 15.4 COI |

## C Clinical Studies:

1. Clinical Sensitivity:

A multi-center clinical study evaluated the clinical performance of the Elecsys EBV IgM assay by testing specimens at three different sites in the US for Elecsys EBV IgM assay and one site with the three comparators. A total of 973 deidentified specimens were tested, of which 721 were prospectively collected from subjects with a laboratory EBV IgM test ordered, and 252 were retrospectively collected specimens from subjects with an EBV IgM test ordered with presumed acute and seronegative results. Of the 973 total specimens, 415 were from pediatric subjects (age ≥2 through ≤21 years) and 558 were from adult subjects (age >21 years). Specimens were classified based on serological marker profile by the comparators. Table 9 presents serological classification of the EBV disease status. Tables 10 through 17 present the positive percent agreement (PPA) and Negative percent agreement (NPA) with 95 % confidence interval (95% CI) by Wilson score method for prospective and retrospective cohorts.

**Table 9. Result interpretation table used to determine the EBV serological status when using Elecsys EBV assays**

| | **Elecsys EBV Assay Results** | | |
|---|---|---|---|
| **EBV Status** | **EBV IgM** | **EBV VCA IgG** | **EBV EBNA IgG** |
| EBV Seronegative | - | - | - |
| Acute Infection | + | - | - |
| | + | + | - |
| Past Infection | - | + | + |
| | - | + | - |
| **Indeterminate EBV Status** [A)] | | | |
| Isolated presence of EBNA IgG | - | - | + |
| Past or Recovery or Reactivation | + | + | + |

[A)] For indeterminate and/or any additional combination of results not shown in this table, further diagnostic testing is recommended

**Table 10. PPA and NPA results for the prospective adult cohort**

| Elecsys EBV IgM | Comparator results | |
|---|---|---|
| | Reactive | Non-reactive |
| Reactive | 5 | 40 |
| Non-reactive | 1 | 451 |
| Total | 6 | 491 |
| | | |
| PPA | 83.30% | 95% CI: 43.7 - 97.0% |
| NPA | 91.90% | 95% CI: 89.1 - 94.0% |

**Table 11. PPA and NPA for the prospective pediatric cohort**

| Elecsys EBV IgM | Comparator results | |
|---|---|---|
| | Reactive | Non-reactive |
| Reactive | 10 | 12 |
| Non-reactive | 2 | 200 |
| Total | 12 | 212 |

| | | |
|---|---|---|
| PPA | 83.30% | 95% CI: 55.2 - 95.3% |
| NPA | 94.30% | 95% CI: 90.4 - 96.7% |

**Table 12. PPA and NPA results for the retrospective adult cohort**

| Elecsys EBV IgM | Comparator results | |
|---|---|---|
| | Reactive | Non-reactive |
| Reactive | 30 | 1 |
| Non-reactive | 0 | 30 |
| Total | 30 | 31 |

| | | |
|---|---|---|
| PPA | 100.00% | 95% CI: 88.7 - 100.0% |
| NPA | 96.80% | 95% CI: 83.8 - 99.4% |

**Table 13. PPA and NPA of the retrospective pediatric cohort**

| Elecsys EBV IgM | Comparator results | |
|---|---|---|
| | Reactive | Non-reactive |
| Reactive | 91 | 10 |
| Non-reactive | 3 | 87 |
| Total | 94 | 97 |
| | | |
| PPA | 96.80% | 95% CI: 91.03- 98.91% |
| NPA | 89.70% | 95% CI: 82.05 - 94.3% |

**Table 14. PPA and NPA of the prospective adult cohort with EBV disease classification**

| EBV Serological Classification (IgM / VCA IgG / EBNA IgG) | PPA Estimate and 95% CI | | | NPA Estimate and 95% CI | | |
|---|---|---|---|---|---|---|
| | n/n | % | CI | n/n | % | CI |
| Seronegative (-/-/-) | n/a | n/a | n/a | 15/16 | 93.8% | (69.8-99.8%) |
| Acute (+/-/-) | 2/2 | 100.0% | (15.8-100.0%) | n/a | n/a | n/a |
| Acute (+/+/-) | 3/3 | 100.0% | (29.2-100.0%) | n/a | n/a | n/a |
| Total Acute | 5/5 | 100.0% | (56.6-100%) | n/a | n/a | n/a |

| | | | | | | |
|---|---|---|---|---|---|---|
| Past Infection (-/+/+) | n/a | n/a | n/a | 409/446 | 91.7% | (88.7-94.1%) |
| Past Infection (-/+/-) | n/a | n/a | n/a | 24/26 | 92.3% | (74.9-99.1%) |
| Total Past Infection | n/a | n/a | n/a | 433/472 | 91.7% | 88.9 - 93.9% |
| Isolated presence of EBNA IgG (-/-/+) | n/a | n/a | n/a | 3/3 | 100.0% | (29.2-100.0%) |
| Transient (+/+/+) | 0/1 | 0.0% | (0.0 - 97.5%) | n/a | n/a | n/a |
| Other Indeterminate (+/-/+) | n/a | n/a | n/a | n/a | n/a | n/a |
| Total Indeterminate | 0/1 | 0.0% | (0.0 - 97.5%) | 3/3 | 100.0% | (29.2 - 100.0%) |
| Overall | 5/6 | 83.3% | (43.7 - 96.9%) | 451/491 | 91.9% | (89.1 - 94.1%) |

**Table 15. PPA and NPA of the retrospective adult cohort with EBV disease classification**

| EBV Serological Status (IgM / VCA IgG / EBNA IgG) | Positive Agreement | | | Negative Agreement | | |
|---|---|---|---|---|---|---|
| | x/y | Estimate (%) | 95% CI | x/y | Estimate (%) | 95% CI |
| Seronegative (-/-/-) | n/a | n/a | n/a | 28/29 | 96.6% | (82.2-99.9%) |
| Acute (+/-/-) | 9/9 | 100.0% | (66.4-100%) | n/a | n/a | n/a |
| Acute (+/+/-) | 21/21 | 100.0% | (83.9-100%) | n/a | n/a | n/a |
| Total Acute | 30/30 | 100.0% | (88.4-100%) | n/a | n/a | n/a |
| Past Infection (-/+/+) | n/a | n/a | n/a | n/a | n/a | n/a |
| Past Infection (-/+/-) | n/a | n/a | n/a | 1/2 | 50.0% | (1.3-98.7%) |
| Total Past Infection | n/a | n/a | n/a | 1/2 | 50.0% | (1.3-98.7%) |
| Isolated Presence of EBNA IgG (-/-/+) | n/a | n/a | n/a | n/a | n/a | n/a |
| Transient (+/+/+) | n/a | n/a | n/a | n/a | n/a | n/a |
| Other Indeterminate (+/-/+) | n/a | n/a | n/a | n/a | n/a | n/a |
| Total Indeterminatec | n/a | n/a | n/a | n/a | n/a | n/a |
| Overall | 30/30 | 100.0% | (88.4-100.0%) | 29/31 | 93.5% | (78.6-99.2%) |

**Table 16. PPA and NPA of prospective pediatric cohort with EBV disease classification**

| EBV Serological Status (IgM / VCA IgG / EBNA IgG) | Positive Agreement | | | Negative Agreement | | |
|---|---|---|---|---|---|---|
| | x/y | Estimate (%) | 95% CI | x/y | Estimate (%) | 95% CI |

| | | | | | | |
|---|---|---|---|---|---|---|
| Seronegative (-/-/-) | n/a | n/a | n/a | 116/118 | 98.3% | (94.0-99.8%) |
| Acute (+/-/-) | 4/4 | 100.0% | (39.8-100.0%) | n/a | n/a | n/a |
| Acute (+/+/-) | 4/6 | 66.7% | (22.3-95.7%) | n/a | n/a | n/a |
| Total Acute | 8/10 | 80.0% | (44.4-97.5%) | n/a | n/a | n/a |
| Past Infection (-/+/+) | n/a | n/a | n/a | 77/86 | 89.5% | (81.1-95.1%) |
| Past Infection (-/+/-) | n/a | n/a | n/a | 6/7 | 85.7% | (42.1-99.6%) |
| Total Past Infection | n/a | n/a | n/a | 83/93 | 89.2% | (81.1-94.7%) |
| Isolated Presence of EBNA IgG (-/-/+) | n/a | n/a | n/a | 1/1 | 100.0% | (2.5-100.0%) |
| Transient (+/+/+) | 2/2 | 100.0% | (15.8-100.0%) | n/a | n/a | n/a |
| Other Indeterminate (+/-/+) | n/a | n/a | n/a | n/a | n/a | n/a |
| Total Indeterminate | 2/2 | 100.0% | (15.8-100.0%) | 1/1 | 100.0% | (2.5-100.0%) |
| Overall | 10/12 | 83.3% | (51.6-97.9%) | 200/212 | 94.3% | (90.3-97.0%) |

**Table 17. PPA and NPA of the retrospective pediatric cohort with EBV disease classification**

| EBV Serological Status (IgM / VCA IgG / EBNA IgG) | Positive Agreement | | | Negative Agreement | | |
|---|---|---|---|---|---|---|
| | x/y | Estimate (%) | 95% CI | x/y | Estimate (%) | 95% CI |
| Seronegative (-/-/-) | n/a | n/a | n/a | 86/89 | 96.6% | (90.5-99.3%) |
| Acute (+/-/-) | 35/38 | 92.1% | (78.6-98.3%) | n/a | n/a | n/a |
| Acute (+/+/-) | 55/55 | 100.0% | (93.5-100.0%) | n/a | n/a | n/a |
| Total Acute | 90/93 | 96.8% | (90.9-99.3%) | n/a | n/a | n/a |
| Past Infection (-/+/+) | n/a | n/a | n/a | 1/2 | 50.0% | (1.3-98.7%) |
| Past Infection (-/+/-) | n/a | n/a | n/a | 0/6 | 0.0% | (0.0-45.9%) |
| Total Past Infection | n/a | n/a | n/a | 1/8 | 12.5% | (0.3-52.7%) |
| Isolated Presence of EBNA IgG (-/-/+) | n/a | n/a | n/a | n/a | n/a | n/a |
| Transient (+/+/+) | 1/1 | 100.0% | (2.5-100.0%) | n/a | n/a | n/a |
| Other Indeterminate (+/-/+) | n/a | n/a | n/a | n/a | n/a | n/a |
| Total Indeterminate | 1/1 | 100.0% | (2.5-100.0%) | n/a | n/a | n/a |
| Overall | 91/94 | 96.8% | (91.0-99.3%) | 87/97 | 89.7% | (81.9-94.9%) |

2. Clinical Specificity:

Not applicable

3. Clinical Cut-Off

See section A.5 for cut-off study

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

Not applicable

## D Expected Values/Reference Range:

**Table 18. Summary of expected values with age and sex**

| Age Group (Years) | Sex | Reactive | | Nonreactive | | Total |
|---|---|---|---|---|---|---|
| | | Number | % | Number | % | Number |
| 2 to <6 years | Female | 6 | 31.6 | 13 | 68.4 | 19 |
| | Male | 8 | 13.3 | 52 | 86.7 | 60 |
| | Not Reported | 1 | 100.0 | 0 | 0.0 | 1 |
| | Total | 15 | 18.8 | 65 | 81.3 | 80 |
| 6 to <11 years | Female | 5 | 14.3 | 30 | 85.7 | 35 |
| | Male | 9 | 17.6 | 42 | 82.4 | 51 |
| | Total | 14 | 16.3 | 72 | 83.7 | 86 |
| 11 to <16 years | Female | 12 | 22.6 | 41 | 77.4 | 53 |
| | Male | 11 | 22.4 | 38 | 77.6 | 49 |
| | Total | 23 | 22.5 | 79 | 77.5 | 102 |
| 16 to <22 years | Female | 50 | 54.9 | 41 | 45.1 | 91 |
| | Male | 22 | 38.6 | 35 | 61.4 | 57 |
| | Total | 72 | 48.6 | 76 | 51.4 | 148 |
| 22-39 years | Female | 17 | 17.2 | 82 | 82.8 | 99 |
| | Male | 27 | 34.6 | 51 | 65.4 | 78 |
| | Total | 44 | 24.9 | 133 | 75.1 | 177 |
| 40-59 years | Female | 12 | 12.8 | 82 | 87.2 | 94 |
| | Male | 9 | 8.3 | 99 | 91.7 | 108 |
| | Total | 21 | 10.4 | 181 | 89.6 | 202 |
| ≥ 60 years | Female | 7 | 9.6 | 66 | 90.4 | 73 |
| | Male | 5 | 4.7 | 101 | 95.3 | 106 |
| | Total | 12 | 6.7 | 167 | 93.3 | 179 |
| | Female | 109 | 23.5 | 355 | 76.5 | 464 |
| | Male | 91 | 17.9 | 418 | 82.1 | 509 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Total | Not Reported | 1 | 100.0 | 0 | 0.0 | 1 |
| | Overall | 201 | 20.6 | 773 | 79.4 | 974 |

## E Other Supportive Instrument Performance Characteristics Data:

**Carry over study:** A carryover study was performed to determine the Elecsys EBV IgM on the cobas e 801 analyzer by running negative and high positive samples at varying sequences. The data demonstrated that there is no carry over effect on the cobas e 801 analyzer.

**Electrical safety and electromagnetic compatibility (EMC)**: EMC testing were performed, and the system was found to be acceptable.

**Software and cybersecurity**: Software and cybersecurity documentation was reviewed and found to be acceptable.

## 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.