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

I Background Information:

A 510(k) Number

K201256

B Applicant

Procise Diagnostics

C Proprietary and Established Names

Procise CRP
ProciseDx Analyzer
ProciseDx Calibration Cartridge

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
DCK	Class II	21 CFR 866.5270 - C-Reactive Protein Immunological Test System	IM - Immunology

II Submission/Device Overview:

A Purpose for Submission:

New assay and new instrument

B Measurand:

C-reactive protein

C Type of Test:

Quantitative, Immunofluorescent

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

The Procise CRP assay is a time-resolved fluorescence energy transfer immunoassay for the quantitative determination of C-Reactive Protein (CRP) levels in human serum. The test is carried out by means of the ProciseDx Analyzer.

Measurement of CRP aids in evaluation of injury to body tissues, infection, and inflammatory disorders. The instrument and assay are for use by trained professionals in the clinical laboratory. For *in vitro* diagnostic use only. Not for point of care use.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

ProciseDx Analyzer

IV Device/System Characteristics:

A Device Description:

The Procise CRP is used to measure CRP level in human serum. The Procise CRP assay system includes the Procise CRP Assay Kit, ProciseDx Calibration Cartridge, and the ProciseDx Analyzer. Each Procise CRP Assay Kit includes Procise CRP reagent cartridges, buffer bulbs, and Procise CRP low and high assay controls as follows.

- Twenty pouched Procise CRP reagent cartridges for single use
- Twenty buffer bulbs
- Two pouched Low assay controls (~ 8mg/L)
- Two pouched High assay controls (~ 45 mg/L)
- Product Insert

The ProciseDx Analyzer is a benchtop instrument designed to test the Procise CRP assay.

B Principle of Operation:

The Procise CRP assay is a homogeneous assay that uses a fluorescence resonance energy transfer (FRET) signal to detect the presence and quantity of CRP. FRET is a process in which a donor molecule, in an excited state, transfers excitation energy to an acceptor fluorophore when

the two are brought into close proximity. Upon excitation at a characteristic wavelength, the energy absorbed by the donor is transferred to the acceptor, which in turn emits light energy. The level of light emitted from the acceptor fluorophore is directly proportional to the degree of donor/acceptor complex formation.

The Procise CRP assay format is designed as a competitive format. A monoclonal anti-CRP antibody and exogenous CRP antigen are labeled with donor and acceptor fluorophores, respectively. The monoclonal antibody specific for CRP is labelled with the donor fluorophores and the CRP antigen is labelled with the acceptor fluorophore. Similar to other competitive assay formats, as the concentration of CRP increases a proportional decrease in the signal is observed.

Blood specimens are collected by venipuncture and allowed to clot. The serum is collected from the clotted blood specimen, and the sample, buffer, and assay chemistry are mixed in a cartridge and loaded into the analyzer. The concentration of CRP is measured by the analyzer.

C Instrument Description Information:

1. Instrument Name:

   ProciseDx Analyzer

2. Specimen Identification:

   It is recommended that the sample is collected in a barcoded serum collection tube. When the sample has been loaded into the cartridge, the collection tube barcode may be scanned into the Sample ID field on the analyzer as described in Specimen Sampling and Handling (#3) below. Alternatively, the Sample ID may be entered manually by using the touch keyboard on the screen.

3. Specimen Sampling and Handling:

   A manual precision pipette is used to dispense 20 µL of sample into the cartridge. The operator obtains a sample, adds the 1.0 mL buffer included in the kit and sample to the cartridge, and inverts the cartridge multiple times to mix sample buffer and reagents. The operator then enters the Operator ID and the Patient ID. Entry may be performed by scanning a barcode on the sample tube or by using the touch keyboard on the screen. When input is complete, the operator presses run and inserts the cartridge when prompted. When a cartridge is inserted in the analyzer, the cartridge barcode is automatically read and this determines the appropriate assay method and associated assay parameters.

4. Calibration:

   Calibration check must be completed at least once every 30 days using ProciseDx Calibration Cartridge. The calibration function is selected from the main menu and the operator enters their User ID, either by scanning a barcode or by using the touch keyboard on the screen. The operator presses run and inserts the Calibration Cartridge when prompted. The Pass/Fail result will be displayed automatically.

5. Quality Control:

- External Low (~ 8mg/L) and High (~ 45 mg/L) Assay Controls included in the kit
- Internal Assay Controls built-in Procise CRP reagent cartridges for two independent readings: optical density (OD) and donor

V Substantial Equivalence Information:

A Predicate Device Name(s):

QuikRead go CRP, QuikRead go CRP Verification Set, QuikRead go CRP Control Set, and QuikRead go Instrument

B Predicate 510(k) Number(s):

K142993

C Comparison with Predicate(s):

Device & Predicate Device(s):	K201256	K142993
Device Trade Name	Procise CRP	QuikRead Go CRP
General Device Characteristic Similarities		
Intended Use/ Indications For Use	The Procise CRP assay is a time-resolved fluorescence energy transfer immunoassay for the quantitative determination of C-Reactive Protein (CRP) levels in human serum. The test is carried out by means of the ProciseDx Analyzer. Measurement of CRP aids in evaluation of injury to body tissues, infection, and inflammatory disorders. The instrument and assay are for use by trained professionals in the clinical laboratory. For *in vitro* diagnostic use only. Not for point of care use.	The QuikRead go CRP test is an immunoturbidimetric assay for the in vitro quantitative determination of C-reactive protein (CRP) in K2-EDTA and lithium heparin whole blood, K2-EDTA and lithium heparin plasma, and in serum samples. The test is carried out by means of the QuikRead go instrument. Measurement of C-reactive protein aids in the evaluation of injury to body tissues, and infection and inflammatory disorders. The instrument and assay are for use by trained professionals in the clinical laboratory. For in vitro diagnostic use only. Not for point-of-care use.
Product Code	DCK	Same
Assay Type	Quantitative	Same
Sample Volume	20 µL	Same

Device & Predicate Device(s):	K201256	K142993
Limit of Quantitation	5.0 mg/L	Same
Calibrators	The reagents are pre-calibrated. The lot-specific calibration cuvette.	Same
Traceability	ERM-DA474/IFCC	Same
Assay Principle	Immunoassay	Same
Assay Controls	Two (2) Levels, ready to use	Same
General Device Characteristic Differences		
Sample Type	Serum	Serum, Venous whole blood (K2-EDTA and Li-Heparin), Plasma (K2-EDTA and lithium heparin)
Technology	Fluorescence resonance energy transfer (FRET)	Immunoturbidimetry
Instrument	ProciseDx Analyzer	QuikRead go Analyzer
Capture Antibody	Fab' anti-CRP antibody	Anti-human CRP F(ab)2 fragment
Reagent Storage	Ambient (15-30°C)	Refrigerated (2-8°C)
Assay Range	5.0–150 mg/L (serum)	5–200 mg/L (plasma and serum) 5–150 mg/L (whole blood)

VI Standards/Guidance Documents Referenced:

- CLSI EP05-A3: Evaluation of Precision of Quantitative Measurement Procedures–Third Edition
- CLSI EP06-2nd Edition Evaluation of the Linearity of Quantitative measurement Procedures: A Statistical Approach – First Edition
- CLSI EP07-3rd Edition: Interference Testing in Clinical Chemistry
- CLSI EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures – Second Edition
- CLSI EP25-A: Evaluation of Stability of In Vitro Diagnostic reagents
- CLSI C28-A3: Defining, Establishing, and Verifying Reference Intervals in the Clinical laboratory- Third Edition
- Guidance for Industry and FDA Staff - Review Criteria for Assessment of C-Reactive Protein (CRP), High Sensitivity C-Reactive Protein (hsCRP) and Cardiac C-Reactive Protein (cCRP) Assays.
- Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices Guidance for Industry and FDA Staff.

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

a. Within-Laboratory Precision:

The within-laboratory precision of the Procise CRP was evaluated based on CLSI guideline EP05-A3. A panel of six serum samples was tested in duplicates per run, two runs per day for 20 days using two reagent lots on two analyzers (each lot per each analyzer). Each sample was tested to generate a total of 160 test results (2 replicates x 2 runs x 20 days x 2 lots = 160). The total SD and CV% calculation was based on the within-run, between-run, between-day, and between-lot data. The results are shown in the table below.

Sample	N	Mean (mg/L)	Within-Run		Between-Run		Between-Day		Between-Lot		Total	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	160	5.9	0.4	6.2	0.0	0.0	0.1	1.2	0.2	3.8	0.4	7.4
2	160	9.2	0.6	6.4	0.0	0.0	0.1	0.7	0.5	5.7	0.8	8.6
3	160	35.5	1.4	3.9	0.7	2.0	0.0	0.0	0.3	0.8	1.6	4.4
4	160	75.1	2.8	3.7	0.8	1.1	0.9	1.2	3.4	4.6	4.6	6.1
5	160	93.5	4.3	4.6	0.0	0.0	2.3	2.5	4.2	4.5	6.4	6.8
6	160	125.6	6.8	5.4	0.0	0.0	2.3	1.9	7.0	5.5	10.0	8.0

b. Site-to-Site Reproducibility:

The reproducibility study of the Procise CRP was conducted at three different sites using five serum samples (three patients and two QCs) with different CRP concentrations across the measuring interval. Within-run, between-run, between-day, between-operator/instrument and site-to-site reproducibility were evaluated. The SDs and %CVs for each sample were calculated based on 180 determinations per sample performed with three replicates per run, two runs per day for five different days on two operators/instruments at three test sites using a single reagent lot (3 replicates x 2 runs x 5 days x 2 instruments x 3 sites = 180). The results are shown in the table below.

Sample	N*	Mean (mg/L)	Within-Run		Between-Run		Between-Day		Between-Instrument		Between-Site		Total	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	179	7.27	0.5	6.6	0.0	0.0	0.0	0.0	0.1	1.6	0.2	2.1	0.6	7.6
2	179	25.3	1.7	6.8	0.0	0.0	0.3	1.3	0.0	0.0	0.7	2.7	2.0	7.8
3	177	72.7	6.2	8.5	0.0	0.0	0.7	0.9	0.0	0.0	0.0	0.0	6.5	9.0
QC1	179	5.53	0.5	8.9	0.0	0.0	0.0	0.0	0.1	0.8	0.3	4.6	0.6	10.0
QC2	178	48.7	4.2	8.6	0.0	0.0	0.0	0.0	0.0	0.0	1.8	3.7	4.5	9.3

* excluded 1-3 outliers out of a total N of 180.

2. Linearity:

The linearity of the Procise CRP was evaluated by testing a series of 11 dilution levels prepared evenly covering the CRP concentration range of 3.6 to 161.0 mg/L by pooling the high and low human serum samples. Each sample dilution was measured in one run with three or four replicates; the mean of the three replicates or four replicates was calculated for each sample. Linear regression analysis was performed based on expected value vs observed CRP value. The linear regression results for nine samples within the measuring interval are shown in the table below.

Range (mg/L)	Slope (95%CI)	Intercept (95% CI)	R^2	Bias (%)
3.6 – 161.0	0.99 (0.97 – 1.00)	0.05 (-0.94 – 1.05)	1.00	-3.3 – 8.1

The results support the linearity of the claimed analytical measuring range for the Procise CRP: 5.0 – 150 mg/L.

3. Analytical Specificity/Interference:

To investigate the performance of the Procise CRP with presence of potential endogenous and exogenous interferents, three pooled human serum samples with various CRP concentrations (12.3, 52.9, and 89.7 mg/L) were prepared and spiked with potential interfering substances. The CRP level in the test samples was measured in three replicates and the %bias in relation to the unspiked sample without interferent was calculated. The acceptance criterion: No significant interference (%bias < 10%), was observed at the concentration of the potential interfering substances shown in the table below.

Endogenous Interferent	Concentration
Hemolysate	300 mg/dL
Triglycerides	37 mmol/L
Bilirubin Conjugated	43 mg/dL
Bilirubin Unconjugated	40 mg/dL
Human anti-mouse Antibodies (HAMA)	200 IU/mL
Rheumatoid Factor	400 IU/mL

Exogenous Interferent	Concentration
Acetaminophen	20 mg/dL
Ascorbic Acid	170 µmol/L
Acetylsalicylic Acid	65 mg/dL
Adalimumab	20 µg/mL
Amoxicillin	400 µmol/L
Ampicillin	500 µmol/L
Caffeine	600 µmol/L
Chloramphenicol	300 µmol/L
Erythromycin	400 µmol/L

Etanercept	0.1 µmol/L
Fluconazole	480 µmol/L
Gentamycin	120 µmol/L
Ibuprofen	2000 µmol/L
Infliximab	20 µg/mL
Methotrexate	1950 µmol/L
Penicillin	150 mg/L
Prednisone	1 µmol/L

4. Assay Reportable Range:

   The assay reportable range of the Procise CRP is 5 to 150 mg/L.

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

   Traceability:

   The calibrators are traceable against ERM-DA474/IFCC.

   Stability:

   Shelf-Life Stability: The real-time reagent stability at ambient room temperatures was evaluated by testing three serum samples (~5, ~50, and ~100 mg/L) in six replicates each, using two lots of the Procise CRP stored at 15°C, 23°C, and 30°C up to 26 months. The results support that the Procise CRP is stable for 24 months at ambient room temperatures of 15–30°C.

   The reagent stability for long-term storage was evaluated by testing ten native and three pooled human serum samples with CRP concentrations ranged 5.0 to 73.3 mg/L, using two reagent lots stored at -80°C. The results support that the Procise CPR is stable for up to 24 months at -80°C. The long-term stability evaluation is ongoing.

   Shipping Stability: The shipping stability was evaluated by testing two serum samples with CRP concentrations around 5 and 50 mg/L, using four pouched Procise CRP Assay kits, each containing 20 Procise CRP cartridges (reagent), 20 buffer bulbs, and 2 pouches of assay controls (low and high). The packed Procise CRP Assay Kits were placed at 38°C for 72 hours and then at 60°C for 6 hours followed by a stress test in a sequence of compression, random vibration, drop (in carton), random vibration, low pressure, and a bubble test. The Procise CPR reagent is stable for up to 72 hours at 38°C followed by 6 hours at 60°C under the simulated shipping conditions.

   Calibration Stability: Stability of the calibration cartridge was evaluated on ProciseDx Analyzer by testing six calibration cartridges stored at 23°C after an initial calibration. The CRP calibration cartridge is stable at 23°C for up to 18.5 months.

   Sample Stability: CRP in serum is stable for 11 days at 20–25°C, 2 months at 4–8°C, and 3 years at -20°C. (Reference: Use of Anticoagulants in Diagnostic Laboratory Investigations. WHO Publication WHO/DIL/LAB/99.1 Rev. 2. 2002, p28.)

6. Detection Limit:

For limit of blank (LoB), a set of four analyte depleted serum samples was investigated using two reagent lots over three days. Each sample was tested in five replicates per run, one run per day for three days to reach a total of 60 measurements per reagent lot. LoB was determined per CLSI EP17-A2. The higher value from both lots was taken for the LoB at 0.9 mg/L. The claimed LoB is 1.1 mg/L.

For limit of detection (LoD), a set of five low level serum samples in the range below the measuring interval was investigated using two reagent lots. Each sample was tested in four replicates per run, one run per day for three days to reach a total of 60 measurements per reagent lot. The LoD was determined per CLSI EP17-A2. The higher value from both lots was taken for the LoD at 1.5 mg/L.

For limit of quantitation (LoQ), a set of five low measurand content serum samples from the lower end of the measuring interval was investigated. Each sample was tested in four replicates per run, one run per day for three days using two lots to reach a total of 24 measurements. The LoQ was determined as 2.0 mg/L following CLSI EP17-A2, the sample with the highest value for the %CV in accordance with the specification for both reagent lots (< 20%). The claimed LoQ is 5.0 mg/L.

7. Assay Cut-Off:

See below for Expected Values/Reference Range

8. Accuracy (Instrument):

The ProciseDx Analyzer accuracy was evaluated using ERM-DA474/IFCC that was serially diluted with CRP-depleted human serum for preparation of 11 dilution levels, ranging 1.0 to 41.2 mg/L CRP. Each diluted serum sample was tested in three replicates while the original ERM-DA474/IFCC (highest concentration) was tested in six replicates. The recovery for all samples was within 100±10% from the expected values based on dilutions of ERM-DA474/IFCC.

9. Carry-Over:

Not applicable, the Procise CRP cartridge is single use.

B Comparison Studies:

1. Method Comparison with Predicate Device:

A total of 81 serum samples spanning the assay measuring interval were tested by both the Procise CRP and a comparator (Orion QuikRead go CRP). Measurement comparison between these two assays was evaluated using Passing-Bablok regression analysis and the result is shown in the table below. At the medical decision point of 5.0 mg/L, the calculated bias was 2.7%.

Sample (N)	Range (mg/L)	Slope (95%CI)	Intercept (95% CI)
81	5.3 – 134.0	0.99 (0.95 – 1.01)	0.20 (-0.56 – 1.16)

2. Matrix Comparison:

Not applicable

C Clinical Studies:

1. Clinical Sensitivity:

Not applicable

2. Clinical Specificity:

Not applicable

D Clinical Cut-Off:

Not applicable

E Expected Values/Reference Range:

The reference range study was conducted by enrolling apparently healthy subjects. The subjects with chronic diseases, including obesity (BMI > 30, https://www.cdc.gov/obesity/about-obesity/index.html) were excluded in the analysis. A total of 170 samples (88 males at 18–72 years and 82 females at 21–69 years) were included in the analysis. Of 170 tested samples, 150 samples (150/170, 88.2%) had concentrations within the consensus reference interval at 5 mg/L taken from the literature reference*. The 95th percentile was 8.2 mg/L. Each laboratory should establish its own reference range.

	Total (n=170)	Male (n=88)	Female (n=82)
Mean	2.6 mg/L	2.0 mg/L	3.2 mg/L
Median	1.2 mg/L	1.0 mg/L	1.8 mg/L
95% percentile	8.2 mg/L	6.1 mg/L	11.0 mg/L
99% percentile	32.5 mg/L	48.7 mg/L	25.9 mg/L

**The expected value in the normal population aged 20 to 60 years is < 5mg/L per literature (Roberts WL, McMillin GA, Burtis CA, Bruns DE. Reference Information for the Clinical Laboratory, Tietz Textbook of Clinical Chemistry and Molecular Diagnostics; 4th Ed., Burtis CA, Ashwood ER, Bruns DE (2006): 2263).*

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.