BECKMAN COULTER

AU/DxC AU US

Instructions For Use

CRP LATEX
CRP Latex

REF OSR6199 4 x 30 mL R1, 4 x 30 mL R2

For *in vitro* diagnostic use only.

For Rx use only

PRINCIPLE

INTENDED USE

System reagent for the quantitative determination of C-Reactive Protein in human serum and plasma on Beckman Coulter AU/DxC AU Analyzers. Measurement of CRP is useful for the detection and evaluation of infection, tissue injury, inflammatory disorders and associated diseases. Measurements may also be useful as an aid in the identification of individuals at risk for future cardiovascular disease. High sensitivity CRP (hsCRP) measurements, when used in conjunction with traditional clinical laboratory evaluation of acute coronary syndromes, may be useful as an independent marker of prognosis for recurrent events, in patients with stable coronary disease or acute coronary syndromes.[1,2]

SUMMARY AND EXPLANATION

C-reactive protein (CRP) is one of the most sensitive acute-phase reactants. With the Beckman Coulter AU/DxC AU System CRP Latex reagent, CRP can be measured down to very low concentrations, depending on the application used (different instrument settings):

1. **Normal Application**: C-reactive protein levels in serum can rise dramatically after myocardial infarction, stress, trauma, infection, inflammation, surgery, or neoplastic proliferation. The increase occurs within 24 to 48 hours, and the level may be 2000 times normal. Because the increase is non-specific, however, it cannot be interpreted without a complete clinical history, and even then only by comparison with previous values.
2. **Highly Sensitive (Cardiac) Application**

   Studies have also shown that the detection of much lower CRP levels can provide valuable information. The typical CRP concentration for healthy adults is (depending on the specific level of the individual patient) < 1 mg/L.[3] Slightly higher values can indicate an increased risk for coronary heart disease in asymptomatic patients.[1,2] CRP concentrations above 3 mg/L, at the time of hospital admission, predict a precarious outcome after a myocardial infarct.[4] The following relative risk categories in relation to average CRP level have been recommended[5]: Low < 1mg/L, Average 1.0 to 3.0 mg/L and High > 3.0 mg/L.

   Increases in C-Reactive Protein values are not specific and should not be interpreted without a complete clinical history since CRP is an acute phase protein which can rise non-specifically due to other inflammatory conditions.

   For cardiac risk analysis, other cardiac disease-specific testing must be done, such as Total cholesterol, HDL cholesterol, and LDL cholesterol. When being used for risk assessment, levels of CRP > 10 mg/L should be evaluated for other non-cardiovascular origins. Testing for any risk assessment should not be performed while there is indication of infection, systemic inflammation, or trauma. This assay is not meant for management of acute coronary syndrome and is not a substitute for traditional cardiovascular risk factors. Screening the entire adult population for hsCRP is not recommended. The average of hsCRP levels determined two weeks apart should be used in performing risk assessment on metabolically stable patients. hsCRP is considered to be a Class IIa marker for acute coronary syndrome in addition to Troponin I.[6]

METHODOLOGY

Immune complexes formed in solution scatter light in proportion to their size, shape, and concentration. Turbidimeters measure the reduction of incidence light due to reflection, absorption or scatter. In this procedure, the measurement of the rate of decrease in light intensity transmitted (increase in absorbance) through particles suspended in solution is the result of complexes formed during the immunological reaction between the CRP of the patient serum and rabbit anti-CRP-antibodies coated on latex particles.

SPECIMEN

SPECIMEN STORAGE AND STABILITY

C-reactive protein specimens are stable for 11 days at 20 - 25°C and 2 months at 4 - 8°C in serum and plasma. For longer storage, freeze serum to -20°C. [7]

Specimen storage and stability information provides guidance to the laboratory. Based on specific needs, each laboratory may establish alternative storage and stability information according to good laboratory practice or from alternative reference documentation.

Additional handling conditions as designated by this laboratory:

SPECIMEN COLLECTION AND PREPARATION

Serum, K2/K3 EDTA and Lithium heparin plasma may be used.

Comparison studies have shown no statistical significant difference between CRP recovery in serum and plasma within the accuracy and precision limits of the assay.

Centrifuge samples containing precipitates before performing the assay.

Additional instructions for patient sample preparation as designated by this laboratory:

Additional type conditions as designated by this laboratory:

REAGENTS

CONTENTS

CRP Latex Reagent

Reagent storage location in this laboratory:

WARNING AND PRECAUTIONS

1. Exercise the normal precautions required for handling all laboratory reagents.
2. Dispose of all waste material in accordance with local guidelines.
3. This product contains material of animal origin. The product should be considered as potentially capable of transmitting infectious diseases.

REACTIVE INGREDIENTS

Final concentration of reactive ingredients:

Glycine buffer	100 mmol/L
Latex coated with anti-CRP Antibodies	< 0.5%
Also contains preservatives.	

⚠ CAUTION

Sodium azide preservative may form explosive compounds in metal drain lines. See NIOSH Bulletin: Explosive Azide Hazard (8/16/76).
To avoid the possible build-up of azide compounds, flush wastepipes with water after the disposal of undiluted reagent. Sodium azide disposal must be in accordance with appropriate local regulations.

GHS HAZARD CLASSIFICATION

Not classified as hazardous

SDS	Safety Data Sheet is available at beckmancoulter.com/techdocs

MATERIALS NEEDED BUT NOT SUPPLIED WITH REAGENT KIT

CRP Latex Calibrator Normal (N) Set (Cat # ODC0026) for the Normal Application.
CRP Latex Calibrator Highly Sensitive (HS) Set (Cat # ODC0027) for the Highly Sensitive Application.
0.9% Saline

Storage location of the Calibrator in this laboratory:

EQUIPMENT AND MATERIALS

For use on the AU480, AU680, AU5800, DxC 500 AU, DxC 500i and DxC 700 AU Beckman Coulter Analyzers.

Storage location of test tubes or sample cups in this laboratory:

REAGENT PREPARATION

The CRP Latex reagents are ready for use. No preparation is required. Agitate gently before use to ensure a uniform suspension of particles. Repeat at weekly intervals thereafter.

REAGENT STORAGE AND STABILITY

1. The unopened reagents are stable until the expiration date printed on the label when stored at 2 - 8°C.
2. Opened bottles of reagent are stable for 90 days when stored in the refrigerated compartment of the analyzer.

INDICATIONS OF DETERIORATION

Gross turbidity or precipitate in R1, or visible signs of microbial growth in the C-Reactive Protein reagents may indicate degradation and warrant discontinuation of use.

Additional storage requirements as designated by this laboratory:

STABILITY OF FINAL REACTION MIXTURE

The Beckman Coulter AU/DxC AU analyzer automatically computes every determination at the same time interval.

CALIBRATION

CALIBRATION INFORMATION

The frequency of calibration for the CRP Latex procedure is every 90 days for the Normal and Highly Sensitive (Cardiac) Applications. Calibration of this CRP Latex procedure is traceable to IFCC (International Federation of Clinical Chemistry) standard ERM DA472.

6 levels are required to calibrate both the CRP Latex Normal and CRP Highly Sensitive (Cardiac) applications. Levels 2 to 6 are provided in the calibrator kits. For the Level 1 calibrator 0.9% saline should be used.

Recalibration of this test is required when any of these conditions exist:

1. A reagent lot number has changed or there is an observed shift in control values.
2. Major preventative maintenance was performed on the analyzer.
3. A critical part was replaced.

QUALITY CONTROL

During operation of the Beckman Coulter AU/DxC AU analyzer, at least two levels of an appropriate quality control material should be tested a minimum of once a day. In addition, controls should be performed after calibration with each new lot of reagent, and after specific maintenance or troubleshooting steps described in the appropriate Beckman Coulter AU/DxC AU analyzer Instructions For Use (IFU) and Reference Manual. Quality control testing should be performed in accordance with regulatory requirements and each laboratory's standard procedure.

Please note that recovery of non-Beckman Coulter controls may vary with reagent lots of immunoassay products, due to the use of non-human materials in the controls.

Location of controls used at this laboratory.

CONTROL NAME	SAMPLE TYPE	STORAGE

TESTING PROCEDURE(S)

A complete list of test parameters and operational procedures are provided in the relevant AU/DxC AU analyzer IFU and Reference Manual.

RESULTS INTERPRETATION

The default unit of measure is mg/L for conversion to SI units (mg/dL) the result is divided by 10.

REPORTING RESULTS

EXPECTED RESULTS

C-Reactive Protein is a non-specific indicator for a wide range of disease processes. Reference intervals may be affected by different factors.

Normal Application

< 5mg/L[8]

Highly Sensitive (Cardiac) Application

Recommended Cardiac risk assessment categories:

Low	< 1 mg/L
Average	1.0 to 3.0 mg/L
High	>3.0 mg/L

Reference Intervals shown above were taken from the literature. Expected values may vary with age, sex, sample type, diet and geographical location. Each laboratory should verify the transferability of the expected values to its own population, and if necessary determine its own reference interval according to good laboratory practice. For diagnostic purposes, results should always be assessed in conjunction with the patient's medical history, clinical examinations and other findings.

Expected reference ranges in this laboratory:

INTERVALS	SAMPLE TYPE	UNITS

Additional reporting information as designated by this laboratory:

PROCEDURAL NOTES

ANTICOAGULANT TEST RESULTS

The following anticoagulants were assessed by Deming regression analysis with a minimum of 40 paired serum and plasma samples. Values of serum (X) ranging from 0.29 mg/L to 9.89 mg/L (cardiac range) for highly sensitive application were compared with the values for plasma (Y) yielding the following results on the DxC 500 AU analyzer.

Application	Highly Sensitive Application (Cardiac)		
Y Method	K2 EDTA	K3 EDTA	Lithium Heparin
X Method	SERUM	SERUM	SERUM
Slope	0.976	0.952	0.983
Intercept	0.037	0.024	-0.009
Y=	0.976x + 0.037	0.952x + 0.024	0.983x - 0.009
Correlation Coeff.(r)	0.9988	0.9960	0.9990

The following anticoagulants were assessed by Deming regression analysis with a minimum of 40 paired serum and plasma samples. Values of serum (X) ranging from 5.31 mg/L to 467.91 mg/L for normal application were compared with the values for plasma (Y) yielding the following results on the DxC 500 AU analyzer.

Application	**Normal Application**		
Y Method	K2 EDTA	K3 EDTA	Lithium Heparin
X Method	SERUM	SERUM	SERUM
Slope	1.008	1.007	1.005
Intercept	-0.384	-0.845	-0.559
Y=	1.008x - 0.384	1.007x - 0.845	1.005x - 0.559
Correlation Coeff.(r)	0.9999	0.9998	0.9999

INTERFERENCES

Normal and Highly Sensitive (Cardiac) Applications
Results of studies[9] show that the following substances may interfere with this C-reactive protein procedure.[10]
Normal Application

Icterus: Interference less than 5% up to 40 mg/dL Bilirubin

Haemolysis: Interference less than 5% up to 5 g/L Haemoglobin

Lipemia: Interference less than 10% up to 1,000 mg/dL Intralipid

Rheumatoid Factor: Interference less than 10% up to 500 IU/mL Rheumatoid Factor

Triglyceride: Interference less than 10% up to 500 mg/dL Triglyceride

Highly Sensitive (Cardiac) Application

Icterus: Interference less than 5% up to 40 mg/dL Bilirubin

Haemolysis: Interference less than 5% up to 5 g/L Haemoglobin

Lipemia: Interference less than 10% up to 1,000 mg/dL Intralipid

Rheumatoid Factor: Interference less than 10% up to 500 IU/mL Rheumatoid Factor

Triglyceride: Interference less than 10% up to 500 mg/dL Triglyceride

* Intralipid, manufactured by Pharmacia, is a 20% fat emulsion used to emulate extremely turbid samples.

Results of studies conducted to evaluate the susceptibility of the method to interference from common or known drugs that could interfere with the CRP Normal and CRP Highly Sensitive (Cardiac) Applications are listed below. The criteria for no significant interference is recovery within 10% of the initial value (sample containing no interferent).

No significant interference is observed from substances up to the following concentrations:

Acetaminophen	15.6 mg/dL
Acetylsalicylic Acid	3 mg/dL
Amoxicillin	5.4 mg/dL
Ascorbic Acid	5.25 mg/dL
Atorvastatin	0.075 mg/dL
Azithromycin	1.11 mg/dL

Cephalexin	12.6 mg/dL
Ciprofloxacin	1.2 mg/dL
Fluconazole	2.55 mg/dL
Ibuprofen	21.9 mg/dL
Lisinopril	0.0246 mg/dL
Metformin	1.2 mg/dL
Methotrexate	136 mg/dL
Naproxen	36 mg/dL
Omeprazole	0.84 mg/dL
Prednisone	0.0099 mg/dL

In very rare cases gammopathy, especially monoclonal IgM (Waldenström's macroglobulinemia), may cause unreliable results.

Samples containing heterophilic antibodies can cause falsely elevated results. Please note that oral contraceptives have been reported to affect results.[11]

The information presented is based on results from Beckman Coulter studies and is current at the date of publication. Beckman Coulter Inc., makes no representation about the completeness or accuracy of results generated by future studies. Further information on interfering substances is available.[12]

Laboratory specific procedure notes:

PERFORMANCE CHARACTERISTICS

PERFORMANCE CHARACTERISTICS

Data contained within this section is representative of performance on Beckman Coulter systems. Data obtained in your laboratory may differ from these values.

DYNAMIC RANGE / ANALYTICAL MEASURING RANGE

The CRP Latex reagent is linear from:

Beckman Coulter AU/DxC AU Analyzers	Assay Range Normal Application	Assay Range Highly Sensitive (Cardiac) Application
AU480/AU680	1.0 to 480 mg/L	0.2 to 160 mg/L
AU5800/DxC 700 AU	1.0 to 480 mg/L	0.2 to 80 mg/L
DxC 500 AU / DxC 500i	5.0 to 480 mg/L	0.2 to 80 mg/L

Normal Application

Samples that are above the linear range of the normal application may be manually diluted 1 in 2 using physiological saline, repeated, and multiplied by the dilution factor.

On the AU480/AU680/AU5800 and DxC 700 AU samples measuring below the measuring range for the normal CRP application should be reported as < 1.0 mg/L.

On the DxC 500 AU and DxC 500i, samples measuring below the measuring range for the normal CRP application should be reported as < 5.0 mg/L.

Highly Sensitive (Cardiac) Application

Samples that are above the linear range of the Highly Sensitive (Cardiac) application may be re-run using the normal application or manually diluted 1 in 2 using physiological saline, repeated, and multiplied by the dilution factor.

Samples measuring below the measuring range for the Highly Sensitive (Cardiac) CRP application should be reported as < 0.2 mg/L.

LIMITATIONS

1. Sample carryover may occur when a high CRP sample >160mg/L is run directly before a sample with low CRP.

   The CRP Latex Assay requires the use of Contamination Prevention Parameters. Please refer to the latest version of the AU480/AU680/AU5800/DxC 700 AU Contamination Prevention Parameters on the Beckman Coulter Website.

   Contamination Prevention Parameters on the DxC 500 AU and DxC 500i are run automatically by the system.

2. **Prozone**

   Normal Application

   Patients with inflammatory and/or infectious conditions should have their CRP measured using the Normal Application, particularly when used for patient monitoring. When using the Normal Application on all Beckman Coulter AU/DxC AU systems, patients with CRP concentrations up to 750 mg/L will not generate false low results within the analytical range.

   Highly Sensitive (Cardiac) Application

   When using the Highly Sensitive (Cardiac) Application on the Beckman Coulter AU480/AU680 systems, patients with CRP concentrations up to 400 mg/L will not generate false low results within the analytical range.

   When using the Highly Sensitive (Cardiac) Application on the Beckman Coulter AU5800, DxC 500 AU, DxC 500i and DxC 700 AU systems, patients with CRP concentrations up to 750 mg/L will not generate false low results within the analytical range.

3. Increases in the C-Reactive Protein values are not specific and should not be interpreted without a complete clinical history. When used for cardiovascular risk assessment, these measurements should be compared to previous C-Reactive Protein values.

SENSITIVITY

Limit of Detection / Limit of Quantitation

The Limit of Detection (LoD) and Limit of Quantitation (LoQ) were determined in accordance with the CLSI EP17-A2 guideline.[13]

On the AU480/AU680/AU5800 and DxC 700 AU, correctly operating systems should exhibit sensitivity less than or equal to 1.0 mg/L for the Normal Application and less than or equal to 0.2 mg/L for the Highly Sensitive (Cardiac) Application.

The following data was obtained on a DxC 700 AU analyzer:

Application	LoD	LoQ
Normal	0.23 mg/L	0.52 mg/L
Highly Sensitive	0.08 mg/L	0.08 mg/L

On the DxC 500 AU and DxC 500i, correctly operating systems should exhibit sensitivity less than or equal to 5.0 mg/L for the Normal Application and less than or equal to 0.2 mg/L for the Highly Sensitive (Cardiac) Application.

The following data was obtained on a DxC 500 AU analyzer:

Application	LoD	LoQ
Normal	0.49 mg/L	0.89 mg/L
Highly Sensitive (Cardiac)	0.03 mg/L	0.06 mg/L

METHODS COMPARISON

Reference[14]

Patient serum samples were evaluated in method comparison studies.

Results of Deming regression analysis were as follows:

DxC 500 AU versus DxC 700 AU

Normal Application	
Y Method	DxC 500 AU
X Method	DxC 700 AU
Slope	0.993
Intercept	0.606
Correlation Coeff. (r)	0.9995
No. of Samples (n)	120
Range (mg/L)	5.16 - 470.45

Highly Sensitive (Cardiac) Application	
Y Method	DxC 500 AU
X Method	DxC 700 AU
Slope	0.990
Intercept	0.0421
Correlation Coeff. (r)	0.9997
No. of Samples (n)	115
Range (mg/L)	0.21 - 72.99

PRECISION

Reference [15,16]

Estimates of precision, based on CLSI recommendations, are consistent with typical performance.

Application	Within-Run Precision	Total Precision
Normal Application	≤5% CV or SD ≤0.20 mg/L	≤10% CV or SD ≤0.25 mg/L
Highly Sensitive (Cardiac) Application	SD ≤ 0.02 mg/L	SD ≤ 0.02 mg/L

Assays of serum pools and control sera were performed and the data reduced following the CLSI guidelines above.

The following data was generated on a DxC 500 AU analyzer:

Normal Application DxC 500 AU				
N= 80	**Within-run**		**Total**	
Mean, mg/L	**SD**	**CV%**	**SD**	**CV%**
5.62	0.04	0.7	0.06	1.1
10.12	0.06	0.6	0.11	1.1
36.18	0.35	1.0	0.56	1.5
248.10	1.49	0.6	2.70	1.1
422.85	3.34	0.8	4.33	1.0

Highly Sensitive Application (Cardiac) DxC 500 AU				
N= 80	**Within-run**		**Total**	
Mean, mg/L	**SD**	**CV%**	**SD**	**CV%**
1.06	0.01	1.2	0.01	1.3
3.01	0.02	0.6	0.03	0.8
9.10	0.08	0.9	0.09	1.0
10.5	0.10	0.9	0.15	1.5
70.0	0.53	0.8	0.73	1.0

ADDITIONAL INFORMATION

DxC 700 AU analyzers require that each reagent application has a standard format of abbreviated Test Name. This Test Name is required to allow automated loading of the calibrator information for each application. Refer to the table below for the Test Name assigned to each application for this assay.

Test Name	Description
CRP1U	CRP Latex (Serum) Normal Application
CRP2U	CRP Latex (Serum) Highly Sensitive (Cardiac) Application

Refer to the Beckman Coulter Chemistry Systems Reagent Guide (BAGUIDE) for specific chemistry information for the AU/DxC AU clinical chemistry systems and guidance on symbols used on all AU/DxC AU product labelling.

Setting Sheet Footnotes

User defined

Lot + Bottle

§ Saline should be used for the Level 1 calibrator.

† Beckman Coulter CRP Latex Calibrator Normal Set Cat No.: ODC0026

† Beckman Coulter CRP Latex Calibrator Highly Sensitive Set Cat No.: ODC0027

* Values set for working in mg/L. To work in mg/dL divide by 10

REVISION HISTORY

Updated Specimen Section

Updated REPORTING RESULTS section

Updated Performance Characteristics section

Updated PROCEDURAL NOTES section

Updated References section

Preceding version revision history

Add DxC 500i instrument to IFU

REFERENCES

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