VITROS Products Chemistry

INSTRUCTIONS FOR USE

hsCRP

VITROS Chemistry Products hsCRP Reagent

High-Sensitivity C-Reactive Protein

REF 6801739

Intended Use

For *in vitro* diagnostic use only.

VITROS Chemistry Products hsCRP Reagent is used on the VITROS 5,1 FS Chemistry System and the VITROS 5600 Integrated System to quantitatively measure C-reactive protein (CRP) in human serum and plasma. CRP is used to evaluate the risk of developing coronary heart disease (CHD). The risk of CHD increases with values of CRP that exceed 3 mg/L.

Summary and Explanation of the Test

C-reactive protein is an acute-phase reactant that reflects low-grade systemic inflammation.[1, 2] Increases in CRP values are non-specific and should not be interpreted without a complete clinical history.[2] CRP measurements may be performed for early detection of infection in pediatrics and risk assessment of coronary heart disease.[1, 3, 4, 5, 6] The risk of CHD increases with values of CRP that exceed 3 mg/L.[5]

The VITROS hsCRP assay is classified as a cardiac C-Reactive Protein (cCRP) assay. Cardiac CRP (cCRP) assays are for use as an aid in the identification and stratification of individuals at risk for future cardiovascular disease. When used in conjunction with traditional clinical laboratory evaluation of acute coronary syndromes, cCRP may be useful as an independent marker of prognosis for recurring events in patients with stable coronary or acute coronary syndrome.[7]

The Centers for Disease Control and Prevention and the American Heart Association have made the following recommendations concerning the use of high sensitivity C-Reactive Protein (hsCRP) for cardiovascular disease risk assessment[5]:

- Measurement of hsCRP should be done twice (averaging results) optimally two weeks apart, on metabolically stable patients, and should be compared to previous values. Testing should not be performed while there is indication of infection, systemic inflammation, or trauma.
- Follow-up testing of patients with elevated CRP values should be performed. Patients with persistently unexplained hsCRP levels above 10 mg/L after repeated testing should be evaluated for non-cardiovascular sources of infection or inflammation.
- Due to within-individual variability, serial measurements of hsCRP should not be used to monitor effects of treatment.
- Screening the entire adult population for hsCRP is not recommended.
- hsCRP is not a substitute for traditional cardiovascular risk factors.
- Application of management guidelines for acute coronary syndromes should not be dependent on hsCRP levels.
- Application of secondary prevention measures should be based on global risk assessment and not depend on hsCRP measurements.

Principles of the Procedure

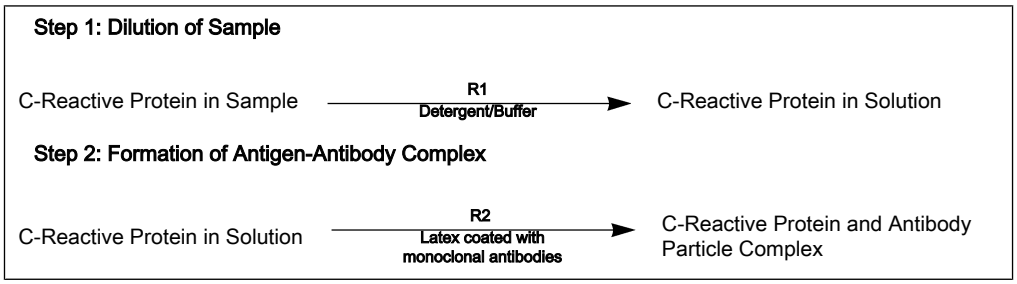
The quantitative measurement of C-reactive protein (CRP) is performed using the VITROS Chemistry Products hsCRP Reagent in conjunction with the VITROS Chemistry Products Calibrator Kit 17 and VITROS Chemistry Products FS Calibrator 1 on the VITROS 5,1 FS Chemistry System and the VITROS 5600 Integrated System. The VITROS Chemistry Products hsCRP Reagent is a dual chambered package containing ready-to-use liquid reagents. Samples, calibrators and controls are mixed with Reagent 1 containing a buffer. Addition of anti-CRP antibodies coupled to latex microparticles (Reagent 2) produces an immunochemical reaction yielding CRP antigen/antibody complexes. The turbidity is measured spectrophotometrically at 660 nm. Once a calibration has been performed for each reagent lot, the CRP concentration in each unknown sample can be determined using the stored calibration curve and the measured absorbance obtained in the assay of the sample.

Test Type and Conditions

Test Type	VITROS System	Approximate Incubation Time	Temperature	Wavelength	Reaction Sample Volume
Two-point Rate	5600, 5,1 FS	8 minutes	37 °C (98.6 °F)	660 nm	16 µL

Not all products and systems are available in all countries.

Reaction Scheme



Warnings and Precautions

For in vitro diagnostic use only.

WARNING: ***This product contains bovine blood components and should be handled using the same precautions as with any other blood or blood-derived product.***

WARNING: ***Take care when handling materials and samples of human origin. Since no test method can offer complete assurance that infectious agents are absent, consider all clinical specimens, controls, and calibrators potentially infectious. Handle specimens, solid and liquid waste, and test components in accordance with local regulations and CLSI Document M29[8] or other published biohazard safety guidelines.***

For specific warnings and precautions for calibrators, quality control materials, and other components, refer to the Instructions for Use for the appropriate VITROS product, or to other manufacturer's product literature.

Reagents

Reactive Ingredients

Reagent 1 (R1): None
Reagent 2 (R2): Latex particles coated with anti-CRP mouse monoclonal antibodies 0.1 % [w/w]

Other Ingredients

Reagent 1 (R1): Buffer, bovine serum albumin, polymer, and preservative
Reagent 2 (R2): Buffer and preservative

Reagent Handling

Caution: **Do not use reagent packs with damaged or incompletely sealed packaging.**

- Inspect the packaging for signs of damage.
- Be careful when opening the outer packaging with a sharp instrument so as to avoid damage to the individual product packaging.
- The reagents are supplied ready for use.
- Avoid agitation, which may cause foaming or the formation of bubbles.

Reagent Preparation

1. Remove from refrigerated storage.
2. Mix thoroughly by gently inverting several times. DO NOT SHAKE.
3. Immediately load into Supply 3.

IMPORTANT: *Do not loosen or remove caps prior to loading.*

Reagent Storage and Stability

VITROS Chemistry Products hsCRP Reagent is stable until the expiration date on the carton when it is stored and handled as specified. Do not use beyond the expiration date.

Reagent	Storage Condition		Stability
Unopened	Refrigerated	2–8 °C (36–46 °F)	Until expiration date
Opened	On-analyzer	System turned on	≤ 4 weeks
	On-analyzer	System turned off	≤ 30 minutes

Verify performance with quality control materials:

- If the system is turned off for more than 30 minutes.
- After reloading reagents that have been removed from Supply 3 and stored for later use.

Specimen Collection, Preparation and Storage

Specimens Recommended

- Serum
- Plasma: Heparin

IMPORTANT: *Certain collection devices have been reported to affect other analytes and tests.*[9] *Owing to the variety of specimen collection devices available, Ortho-Clinical Diagnostics is unable to provide a definitive statement on the performance of its products with these devices. Confirm that your collection devices are compatible with this test.*

Specimens Not Recommended

Plasma:

- EDTA
- Citrate

Serum and Plasma

Specimen Collection and Preparation

Collect specimens using standard laboratory procedures.[10, 11]

Note: For details on minimum fill volume requirements, refer to the operating instructions for your system.

Patient Preparation

No special patient preparation is necessary.

Special Precautions

- Refer to “Sample Dilution” for dilution instructions.
- Centrifuge specimens and remove the serum from the cellular material within two hours of collection.[12]

Specimen Handling and Storage

- Handle and store specimens in stoppered containers to avoid contamination and evaporation.
- Mix samples by gentle inversion and bring to room temperature, 18–28 °C (64–82 °F), prior to analysis.

Specimen Storage and Stability[12]

Storage	Temperature	Stability
Original Specimen		
Room temperature	18–28 °C (64–82 °F)	≤ 4 hours
Refrigerated	2–8 °C (36–46 °F)	≤ 3 days
Frozen	≤-18 °C (≤0 °F)	≤ 6 months

Testing Procedure

Materials Provided

VITROS Chemistry Products hsCRP Reagent

Materials Required but Not Provided

- VITROS Chemistry Products Calibrator Kit 17
- VITROS Chemistry Products FS Calibrator 1
- VITROS Chemistry Products FS Diluent Pack 2 (BSA/Saline) (for calibration only)
- Quality control materials, such as VITROS Chemistry Products hsCRP Performance Verifier I, II and III

Operating Instructions

- Check reagent inventories at least daily to ensure that quantities are sufficient for the planned workload.
- For additional information, refer to the operating instructions for your system.

IMPORTANT: *Bring all fluids and samples to room temperature, 18–28 °C (64–82 °F), prior to analysis.*

Sample Dilution

Do not dilute samples where CRP concentration exceeds the VITROS Chemistry Products hsCRP assay measuring (reportable) range. For these samples, use an alternate method such as VITROS Chemistry Products CRP Slides.

Calibration

Required Calibrators

- VITROS Chemistry Products Calibrator Kit 17
- VITROS Chemistry Products FS Calibrator 1

Calibrator Preparation, Handling, and Storage

Refer to the Instructions for Use for VITROS Chemistry Products Calibrator Kit 17 and VITROS Chemistry Products FS Calibrator 1.

Calibration Procedure

Refer to the operating instructions for your system.

When to Calibrate

Calibrate:

- When the reagent lot number changes.
- When critical system parts are replaced due to service or maintenance.
- When government regulations require.
  For example, in the USA, CLIA regulations require calibration or calibration verification at least once every six months.

The VITROS hsCRP assay may also need to be calibrated:

- If quality control results are consistently outside acceptable range.
- After certain service procedures have been performed.

For additional information, refer to the operating instructions for your system.

Calculations

Absorbance is measured at 660 nm after a fixed incubation time. Once a calibration has been performed for each reagent lot, CRP concentration in the unknown samples can be determined using the stored calibration curve and the measured absorbance obtained in the assay of each sample.

Validity of a Calibration

Calibration parameters are automatically assessed by the system against a set of quality parameters detailed in the Review Assay Data screen (found via Options → Review/Edit Calibrations → Review Assay Data). Failure to meet any of the pre-defined quality parameters results in a failed calibration. The calibration report should be used in conjunction with quality control results to determine the validity of a calibration.

Measuring (Reportable) Range

	Conventional and SI Units (mg/L)
Serum	0.10–15.00

For out-of-range samples, refer to “Sample Dilution.”

Traceability of Calibration

Values assigned to the VITROS Chemistry Products Calibrator Kit 17 and VITROS Chemistry Products FS Calibrator Kit 1 for C-reactive protein are traceable to ERM-DA470 Reference Material.[13]

Quality Control

Quality Control Material Selection

IMPORTANT: *VITROS Chemistry Products hsCRP Performance Verifiers are recommended for use with the VITROS 5,1 FS Chemistry and VITROS Integrated Systems. Evaluate the performance of other commercial control fluids for compatibility with this assay before using for quality control.*

Control materials other than VITROS Chemistry Products hsCRP Performance Verifiers may show a difference when compared with other hsCRP methods if they:

- Depart from a true human matrix.
- Contain high concentrations of preservatives, stabilizers, or other nonphysiological additives.

Quality Control Procedure Recommendations

- Choose control levels that check the clinically relevant range.
- Analyze quality control materials in the same manner as patient samples, before or during patient sample processing.
- To verify system performance, analyze control materials:
  - After calibration.
  - According to local regulations or at least once each day that the assay is being performed.
  - After specified service procedures are performed. Refer to the operating instructions for your system.
- If control results fall outside your acceptable range, investigate the cause before deciding whether to report patient results.
- For general quality control recommendations, refer to CLSI *Statistical Quality Control for Quantitative Measurements: Principles and Definitions; Approved Guideline–Third Edition*[14] or other published guidelines.
- For additional information, refer to the operating instructions for your system.

Quality Control Material Preparation, Handling, and Storage

Refer to the Instructions for Use for VITROS Chemistry Products hsCRP Performance Verifiers I, II and III or to other manufacturer's product literature.

Results

Reporting Units and Unit Conversion

The VITROS 5,1 FS Chemistry and VITROS Integrated Systems may be programmed to report CRP results in conventional, SI, and alternate units.

Conventional and SI Units	Alternate Units
mg/L (mg/dL x 10)	mg/dL (mg/L x 0.1)

Limitations of the Procedure

Known Interferences

None identified.

Other Limitations

- No antigen excess effect was observed for samples with C-reactive protein concentrations up to 360 mg/L.
- Samples that generate a Sample Integrity T-index flag and are above the measuring (reportable) range should be assayed by an alternative method, such as the VITROS Chemistry Products CRP Slide assay. Refer to the operating instructions for additional information concerning Sample Integrity flags.
- Samples that generate a Sample Integrity T-index flag and are within the measuring (reportable) range will be negatively biased by >15%. These samples may be diluted with equal parts of human serum containing a low concentration of C-reactive protein and retested.
- Certain drugs and clinical conditions are known to alter C-reactive protein concentration *in vivo*. For additional information, refer to one of the published summaries.[15, 16, 17, 18, 19, 20, 21]
- Heterophilic, e.g. human anti-mouse, antibodies in the serum or plasma of certain individuals are known to cause interference with immunoassays.[22] These antibodies may be present in blood samples from individuals regularly exposed to animals or who have been treated with animal serum products.

Interpretation of Results and Expected Results

Reference Interval

These guidelines have been recommended by the U.S. Centers for Disease Control and Prevention, and the American Heart Association for assessment of risk for cardiovascular disease in adults.[5]

Classification for Cardiovascular Disease Risk	Conventional and SI Units (mg/L)
Low	<1.0
Average	1.0–3.0
High	>3.0–10.0
Indeterminant*	>10.0

* May be an indication of another source of inflammation or infection.

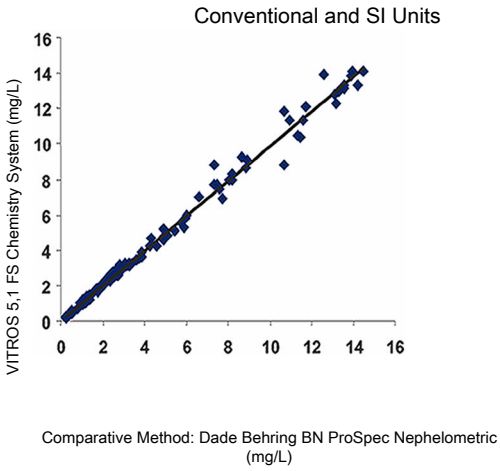
As CRP is a non-specific indicator for a wide range of disease processes, and as reference intervals may vary for each population studied, each laboratory should confirm the validity of these intervals for the population it serves.
Increases in CRP values are non-specific and should not be interpreted without a complete clinical history. Recent medical events resulting in tissue injury, infections, or inflammation, which may cause elevated CRP levels, should be considered.
Follow-up testing of patients with elevated CRP values should be performed. Patients with persistently unexplained CRP levels above 10 mg/L after repeated testing should be evaluated for non-cardiovascular sources of infection or inflammation.
When using CRP to assess the risk of coronary heart disease, measurement of hsCRP should be done twice (averaging results) optimally two weeks apart, on metabolically stable patients, and should be compared to previous values. Testing should not be performed while there is indication of infection, systemic inflammation, or trauma.

Performance Characteristics

Method Comparison

The plots and table show the results of a comparison of serum samples analyzed on the VITROS 5,1 FS Chemistry System with those analyzed using the comparative method, Dade Behring BN ProSpec Nephelometric Method with CRM 470 Calibration.[23]

The table also shows the results of comparisons with serum and plasma samples on the VITROS 5600 Integrated System and the VITROS 5,1 FS Chemistry System. Testing followed NCCLS Protocol EP9.[24]



	n	Slope	Correlation Coefficient	Conventional and SI Units (mg/L) Range of Sample Conc.	Intercept	Sy.x
5,1 FS vs. comparative method	103	0.98	0.995	0.25–14.25	0.049	0.40
5600 vs. 5,1 FS	100	0.98	1.000	0.11–14.68	0.016	0.12

Precision

Precision was evaluated with quality control materials on the VITROS 5,1 FS Chemistry System following NCCLS Protocol EP5.[25] Precision was also evaluated with quality control materials on the VITROS 5600 Integrated System following NCCLS Protocol EP5.[26]

These results are guidelines. Variables such as instrument maintenance, environment, reagent storage/handling, control material reconstitution, and sample handling can affect the reproducibility of test results.

	Conventional and SI Units (mg/L)					
	Mean Conc.	Within Day SD*	Within Lab SD**	Within Lab CV%**	No. Observ.	No. Days
5,1 FS	0.60	0.014	0.030	5.0	80	20
	1.84	0.018	0.038	2.1	80	20
	10.64	0.124	0.187	1.8	80	20
5600	0.40	0.014	0.019	4.8	88	22
	1.44	0.018	0.020	1.4	88	22
	8.14	0.046	0.094	1.2	88	22

* Within Day precision was determined using two runs per day with two replications per run.

** Within Lab precision was determined using a single lot of reagents and at least four calibrations.

Specificity

Substances that Do Not Interfere

Rheumatoid factor (RF) up to 1200 IU/mL does not interfere.

The substances listed in this table were tested on the VITROS Chemistry Products hsCRP assay at a nominal C-reactive protein concentration of 3 mg/L using protocols based on NCCLS Protocol EP7,[27] and found not to interfere, bias <0.28 mg/L, at the concentrations shown.

Compound	Concentration	
Acetaminophen	20 mg/dL	1 mmol/L
N-Acetyl-L-cysteine	100 mg/dL	6.13 mmol/L
Amoxicillin	20 µg/mL	1.15 mmol/L
Ascorbic acid	3 mg/dL	171 µmol/L
Bilirubin	50 mg/dL	0.85 mmol/L
Carbamazepine	120 µg/mL	508 µmol/L
Dipyrone	30 mg/dL	0.85 mmol/L
Ethamsylate	3 mg/dL	0.11 mmol/L
Gentamicin sulfate	120 µg/mL	251 µmol/L
Hemoglobin	1000 mg/dL	10 g/L
Ibuprofen	400 µg/mL	2 µmol/L
Lidocaine	60 µg/mL	2.6 µmol/L
Methotrexate	40 µmol/L	40 µmol/L
Procainamide	100 µg/mL	368 µmol/L
Propanolol	5 µg/mL	19 µmol/L
Rantidine	200 µg/mL	637 µmol/L
Salicylic acid	50 mg/dL	4 mmol/L
Simvastatin	16 µg/mL	1.2 mmol/L
Theophylline	25 mg/dL	1 mmol/L
Valproic acid	500 µg/mL	3 mmol/L

References

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Glossary of Symbols

The following symbols may have been used in the labeling of this product.

Do Not Reuse	Upper Limit of Temperature	Range
Use by or Expiration Date (Year-Month-Day)	Lower Limit of Temperature	Range of Means
LOT Lot Number	Temperature Limitation	Midpoint
SN Serial Number	Consult Instructions for Use	Revised
REF Catalog Number or Product Code	Attention: The Instructions For Use (IFU) has been updated	Supersedes
Attention: See Instructions for Use	S1 For use in Slide Supply 1	Xi Irritant
Manufacturer	S2 For use in Slide Supply 2	Xn Harmful
EC REP Authorized Representative in the European Community	SI SI Units	T Toxic
Σ n Contains Sufficient for "n" Tests	CONV Conventional Units	C Corrosive
IVD *In vitro* Diagnostic Medical Device	Value	F Flammable
	Der Grüne Punkt (the Green Dot). Manufacturer follows certain packaging material waste disposal management regulations	σ Estimate within-lab SD

Revision History

Date of Revision	Version	Description of Technical Changes*
2008-11-06	4.0	• Added information for the VITROS 5600 Integrated System • Test Type and Conditions – Added statement • Traceability of Calibration – Reference material name changed • Method Comparison – Added information on sample types • References – Updated • Glossary of Symbols – Updated • Minor wording and formatting changes
2006-12-21	3.0	• Minor formatting updates • Summary and Explanation of the Test – Added definition of cCRP assays • References – Added FDA cCRP reference; updated M29, H4 and C24.
2005-04-25	2.0	• Reference Interval – updated values • Reporting Units and Unit Conversion –wording update • Precision – wording update
2005-01-13	1.1	Method Comparison - Minor Correction
2004-09-15	1.0	First release of document

* The change bars indicate the position of a technical amendment to the text with respect to the previous version of the document.

When this Instructions For Use is replaced, sign and date below and retain as specified by local regulations or laboratory policies, as appropriate.

_____
Signature

_____
Obsolete Date

CE

EC REP

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