BECKMAN COULTER

CE 2797

AU/DxC AU
Instructions For Use

IgE
Total Immunoglobulin E

REF C22529 1 x 41.5 mL R1
1x 15.5 mL R2
6 x 2 mL IgE Calibrator (Levels 1-6)

For *In Vitro* Diagnostic Use

FOR PROFESSIONAL USE ONLY

For Rx use only

PRINCIPLE

INTENDED USE

The IgE assay is intended for use in the quantitative determination of Total Immunoglobulin E (IgE) concentration in human serum and plasma (lithium heparin, sodium heparin, K_2 EDTA, K_3 EDTA) on Beckman Coulter AU/DxC AU clinical chemistry analyzers. The determination aids in the diagnosis of IgE-mediated allergic disorders in conjunction with other clinical findings. For in vitro diagnostic use only.

SUMMARY AND EXPLANATION

IgE is a member of the immunoglobulin family of proteins that was first described in the 1960's.[1,2] IgE, like all immunoglobulins, is produced by plasma cells in response to antigenic stimuli. IgE is unique however in certain structural aspects and the role it plays in allergic diseases.

Measurement of total serum IgE is often used as a tool in the diagnosis and management of atopic diseases such as asthma, allergic rhinitis, atopic dermatitis and urticaria. It has been used to distinguish atopic from non-atopic individuals presenting allergy-like symptoms.[3] In addition, studies have also shown that increased levels of IgE in cord blood and infants may be predictive of future atopic tendencies.[4,5]

Normal levels of circulating IgE are extremely low in comparison to other immunoglobulins. Levels of IgE at birth are almost undetectable but increase in non-allergic adults.[6] Elevated levels are commonly seen in cases of allergic diseases, parasitic infections, pulmonary aspergillosis, and hyper-IgE syndrome.[3,7,8,9,10]

Serum IgE levels may vary as a result of diet, genetic background, geographical location and other factors. It is therefore recommended that total IgE measurements be used in conjunction with other clinical tests when establishing diagnoses.[11]

METHODOLOGY

Anti-IgE antibody-coated particles bind to IgE in the serum/plasma patient sample resulting in the formation of insoluble aggregates, measured by turbidity. The amount of particle aggregation correlates with the concentration of IgE in the sample. The change in absorbance is measured at 800 nanometers.

CHEMICAL REACTION SCHEME

IgE (sample) + Particle-bound anti-IgE (monoclonal antibody) → [IgE (sample) - Particle Mab Complex]

SPECIMEN

SPECIMEN STORAGE AND STABILITY

Tubes of blood are to be kept closed at all times and in a vertical position. It is recommended that the serum or plasma be physically separated from contact with cells within two hours from the time of collection.[12]

Serum and plasma samples are stable for up to 8 hours when stored at 20°C to 25°C, 7 days when stored at 2°C to 8°C, and up to 60 days when frozen at -15°C to -20°C. Frozen samples should be thawed only once. Analyte deterioration may occur in samples that are repeatedly frozen and thawed.[12]

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.

SPECIMEN COLLECTION AND PREPARATION

Serum samples are recommended. Plasma samples (K_2 EDTA, K_3 EDTA, Lithium Heparin, Sodium Heparin) can be used. Serum or plasma samples should be collected in the manner routinely used for any clinical laboratory test.[13] Anticoagulants tested are listed in the PERFORMANCE CHARACTERISTICS section of the information for use.

REAGENTS

CONTENTS

Each kit contains the following items:

KIT COMPONENTS	QUANTITY
IgE R1 Bottle (Reaction Buffer)	1
IgE R2 Bottle (Antibody Reagent)	1
IgE Calibrator	6
Value Assignment Sheet	1

WARNING AND PRECAUTIONS

- For in vitro diagnostic use
- Human source material used in the preparation of the reagent has been tested and found negative or non-reactive for Hepatitis B, Hepatitis C (HCV), and Human Immunodeficiency Virus (HIV-1 and HIV-2). Because no known test method can offer complete assurance that infectious agents are absent, the product should be handled as if capable of transmitting infectious disease.[14]

REACTIVE INGREDIENTS

REAGENT CARTRIDGE CONSTITUENTS	VOLUME
IgE Antibody (particle-bound mouse anti-IgE antibody)	15.5 mL
Reaction Buffer	41.5 mL
Sodium Azide (used as a preservative)	<0.1% (w/w)

Also non-reactive chemicals necessary for optimal system performance.

CALIBRATOR CONSTITUENTS	
Normal Human Plasma spiked with Cell Culture Human IgE	6 x 2 mL
Sodium Azide (used as a preservative)	<0.1% (w/w)
Bovine Serum Albumin (BSA)	6.0%

Also non-reactive chemicals necessary for optimal system performance.

⚠ 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

At least two levels of control material

Deionized Water

REAGENT PREPARATION

The reagents are ready for use and can be placed directly on board the analyzer.

REAGENT STORAGE AND STABILITY

Stability	
Unopened at 2°C to 8°C	Up to stated expiration date
Onboard analyzer	28 days

- Closed vial shelf life per stability study: 24 months.
- Do Not Freeze
- Storage conditions other than those recommended may cause erroneous results

INDICATIONS OF DETERIORATION

Visible signs of microbial growth, gross turbidity, precipitate, or change in reagent color may indicate degradation and warrant discontinuation of use.

CALIBRATION

CALIBRATOR PREPARATION

No preparation is required.

CALIBRATOR STORAGE AND STABILITY

Stability	
Unopened at 2°C to 8°C	Up to stated expiration date
After opening at 2°C to 8°C if stored capped in the original container	45 days

- Do Not Freeze
- Storage conditions other than those recommended may cause erroneous results
- Re-calibration is recommended if abnormalities are identified by visual inspection of the calibration curve (e.g. switched calibrator levels, higher or lower than expected absorbance at calibrator levels)

CALIBRATION INFORMATION

Calibrators are included in the kit.

An active calibration curve is required for all tests. For the IgE assay, calibration is required every 14 days. Refer to the appropriate system manuals and/or Help system for information on calibration method, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Recalibration	
Required	Not Required
-Change in reagent bottle	-Routine maintenance
-Change in reagent lot	

Recalibration	
Required	Not Required
-Non-routine maintenance	
-Expired calibration curve	

NOTICE

Calibrators are lot-specific and provided as a set for a specific lot of reagent. Do not interchange calibrator and reagent lots.

CALIBRATOR ASSIGNED VALUES

The assigned values for the IgE Calibrator were determined using a matrix of multiple instruments, runs and replicates. For calibrator assigned values, see the Value Assignment Sheet provided in the Reagent Kit.

TRACEABILITY

The analyte in the IgE Calibrators is traceable to the WHO 3rd International Standard for human serum Immunoglobulin E (IgE), 11/234.[15] The traceability process is based on ISO 17511.

QUALITY CONTROL

It is recommended that at least two levels of control material be analyzed daily. Controls should also be run with each new calibration, with a new lot of reagent, and after specific maintenance or troubleshooting as detailed in the Operations Manual. More frequent use of controls or the use of additional controls is left to the discretion of the user based on work load and work flow. Discrepant quality control results should be evaluated by your facility.

TESTING PROCEDURE(S)

PROCEDURE

1. A complete list of test parameters and operational procedures are provided in the relevant AU/DxC AU analyzer IFU and Reference Manual.
2. The setting sheet for Total IgE for each AU/DxC AU instrument model contains the specific settings for the IgE assay, including required data check parameters.
3. Refer to the AU/DxC AU Contamination Prevention Parameters for any applicable settings.
4. Refer to the appropriate system manuals and/or Help system for a specific description of installation, start-up, principles of operation, system performance characteristics, operating instructions, operational limitations and precautions, hazards, maintenance, and troubleshooting.
5. The system unit of measure for sample results is IU/mL.
6. Use 3.2 µL of sample for each determination in addition to the sample container and system dead volumes when requesting the IgE assay. Refer to the appropriate system manuals and/or Help system for the minimum sample volume required.
7. Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.

LIMITATIONS

1. This product is for use on AU/DxC AU Chemistry Systems only.

2. The IgE results should be interpreted in light of the total clinical presentation of the patient, including: symptoms, clinical history, data from additional tests, and other appropriate information.
3. Samples can be accurately measured within the analytical range of the assay (20 to 500 IU/mL). Samples less than 20 IU/mL will be flagged “G” and should be reported as “<20 IU/mL”.
4. Samples in the >500 – 1,000 IU/mL range will be flagged "F" and can be automatically repeated on the system by implementing a Pre-Dilution Rate of 10 when the "F" flag occurs. An approximate concentration result is obtained from auto-dilution of samples in the >500 – 1,000 IU/mL range. Auto-dilution of samples above 1,000 IU/mL is not supported.
5. Samples with IgE concentration in the 1,000 – 7,500 IU/mL range require implementation of data check parameters and generate a "Z" flag or both "F" and "Z" flags, if an excess of antigen is detected in the sample. Samples with IgE concentration in the 1,000 – 7,500 IU/mL range can be diluted manually with deionized water starting at 1:10 or 1:100 and repeated to estimate concentration. Multiply the result by the appropriate dilution factor.
6. Data check parameters are provided to protect from incorrect results due to prozone. However, incorrect result may occur above 7,500 IU/mL, even in the presence of data check parameters. All samples suspected to be above 7,500 IU/mL concentration, based on clinical presentation of the patient or other factors, should be manually diluted to a concentration within the initial analytical range and rerun. The resulting value should be multiplied with the dilution factor to calculate an approximate result.
7. Very high IgE samples may generate false low results that may be flagged "G." Samples suspected to have high concentration may be diluted manually starting at 1:100 and repeated to estimate concentration. Multiply the result by the dilution factor.
8. Patients with high levels of rheumatoid factor or anti-human IgE autoantibodies may falsely elevate IgE results.[16]
9. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce human anti-animal antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other antibodies such as human anti-goat antibodies may be present in patient samples.[17,18] Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.
10. Samples with extremely abnormal optical characteristics, including turbidity, interfere with test results. Extremely turbid samples should not be run.
11. Falsely decreased results may occur in patients being treated with omalizumab.[19]

RESULTS INTERPRETATION

The default unit of measure is IU/mL.

REPORTING RESULTS

This IgE procedure is linear from 20 to 500 IU/mL. Samples exceeding the upper limit of linearity in the IgE concentration range 500 to 1,000 IU/mL should be diluted with deionized water and repeated. The result is multiplied by the dilution factor automatically utilizing the AUTO REPEAT RUN.

EXPECTED RESULTS

The Reference Intervals listed below were taken from literature.[20]

Serum	
0 - <7 y	<25 - 440 IU/mL
7 - <19 y	<25 - 450 IU/mL
Adult (20 – 60 y)	0 - 160 IU/mL

Expected values may vary with age, sex, sample type, diet and geographical location. [11] 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. Refer to guidelines on establishing laboratory-specific reference intervals.[21,22]

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.

LINEARITY

The IgE assay demonstrated acceptable linearity throughout the analytical measuring range of 20 to 500 IU/mL. Based on CLSI EP06-A[23], one high sample (approximately 576 IU/mL) and one low sample (13 IU/mL) were mixed to make a total of 15 sample concentrations evenly distributed across the analytical measuring range.

ANALYTICAL SENSITIVITY

SENSITIVITY

The Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ) were determined in accordance with the CLSI EP17-A2 guideline[24]. Correctly operating AU Systems should exhibit an LoB less than or equal to 10 IU/mL, LoD less than or equal to 15 IU/mL and LoQ less than or equal to 20 IU/mL.

The following data was obtained on a DxC 700 AU Chemistry System using IgE depleted serum and patient samples:

LoB	7.5 IU/mL
LoD	13.8 IU/mL
LoQ	19.6 IU/mL with 11.9% CV

The LoB claim corresponds to the concentration below which IgE-free samples are found with 95% confidence. The LoD claim corresponds to the IgE concentration above the LoB that is detectable with 95% confidence. The LoQ claim corresponds to the IgE concentration that can be quantitatively determined with ≤ 20% CV.

CROSS REACTIVITY

The monoclonal antibody used is highly specific for immunoglobulin E. No cross-reactivities with the immunoglobulins G, A, D and M were detected.

METHODS COMPARISON

A comparison of values using the IgE assay on the DxC 700 AU Chemistry System and a commercially available chemiluminescent immunoassay method gave the following statistical data using weighted Deming regression correlation, following the CLSI EP09c ED3 guideline[25]:

n	*Range of Observations (IU/mL)	Intercept (IU/mL) [95% CI]	Slope [95% CI]	Correlation Coefficient (r)
136	25 to 499	1.0 [-1.0 to 3.0]	0.966 [0.950 to 0.981]	0.996

*as measured by the comparable method

SAMPLE TYPE EQUIVALENCE

A comparison of values obtained by assaying pairs of serum and plasma samples using the IgE assay on the DxC 700 AU Chemistry System gave the following statistical data using Deming regression analysis following the CLSI EP09c ED3 guideline[25]. Serum observations ranged from 24 to 492 IU/mL.

Anticoagulant	n	Intercept (IU/mL) [95% CI]	Slope (95% CI)	Correlation Coefficient (r)
K_2-EDTA	55	-1.7 [-3.4 to -0.1]	0.986 [0.965 to 1.01]	0.997
K_3-EDTA	53	-2.4 [-3.7 to -1.1]	0.964 [0.948 to 0.981]	0.998
Lithium Heparin	55	-0.5 [-1.6 to 0.6]	0.989 [0.975 to 1.00]	0.999
Sodium Heparin	55	0.006 [-1.0 to 1.0]	0.989 [0.976 to 1.00]	0.999

IMPRECISION

The IgE assay exhibits total imprecision ≤ 7.5% at concentrations greater than 93.3 IU/mL and total standard deviation (SD) ≤ 7.0 IU/mL at concentrations ≤ 93.3 IU/mL.

The IgE assay exhibits within run imprecision of ≤ 7.0% at concentrations greater than 71.4 with a standard deviation (SD) ≤ 5.0 IU/mL at concentrations ≤ 71.4 IU/mL.

One study, using commercially available controls and sample pools generating a total of five samples 80 replicates per assay, over 20 days provided the following data on a DxC 700 AU Chemistry Analyzer, calculated based on CLSI EP05-A3[26] guidelines.

SAMPLE TYPE	Mean IgE (IU/mL)	Repeatability (Within-run)		Between-Run		Between-Day		Between-Lot		Between Instrument		Total Precision	
		SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV
Control Level 1	113.5	1.9	1.7	0.0	0.0	1.5	1.3	1.8	1.6	1.0	0.9	2.3	2.0
Control Level 2	229.4	2.3	1.0	0.0	0.0	3.1	1.3	5.7	2.5	3.2	1.4	3.7	1.6
Low Serum Pool	70.4	2.1	3.0	0.4	0.6	0.9	1.3	2.2	3.1	1.5	2.1	2.3	3.3
Mid Serum Pool	167.9	2.4	1.4	0.9	0.5	3.0	1.8	4.6	2.8	0.8	0.5	4.0	2.4
High Serum Pool	413.6	3.9	0.9	0.0	0.0	4.2	1.0	12.1	2.9	5.6	1.4	5.7	1.4

INTERFERING SUBSTANCES

Endogenous substances

Results of studies conducted to evaluate the susceptibility of the method to interference from endogenous substances that could interfere with the assay are listed below. Values were calculated as described in CLSI EP07-A2.[27] The criterion for no significant interference is recovery within 10 IU/mL or 10% of the sample containing no interferent. No significant interference is observed from substances up to the following concentrations:

Hemoglobin	1,000 mg/dL
Lipemia (Intralipid)	1,000 mg/dL
Rheumatoid Factor	250 IU/mL
Unconjugated Bilirubin	60 mg/dL

Drugs and Exogenous Substances

Results of studies conducted to evaluate the susceptibility of the method to interference from common or known drugs and exogenous substances that could interfere with the assay are listed below.[28,29] The criterion for no significant interference is recovery within 10 IU/mL or 10% of the sample containing no interferent.

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

Acetaminophen	15.6 mg/dL
Acetylcysteine	15 mg/dL
Acetylsalicylic acid	3 mg/dL
Ampicillin-Na	7.5 mg/dL
Cefoxitin	660 mg/dL
Cetirizine	0.435 mg/dL
Cyclosporine	0.18 mg/dL
Diphenhydramine	0.0774 mg/dL
Doxycycline	1.8 mg/dL

Fexofenadine	0.116 mg/dL
Heparin	330 units/dL
Ibuprofen	21.9 mg/dL
Levodopa	0.75 mg/dL
Methyldopa	2.25 mg/dL
Metronidazole	12.3 mg/dL
Mometasone	0.000045 mg/dL
Phenylbutazone	32.1 mg/dL
Prednisolone	0.12 mg/dL
Rifampicin	4.8 mg/dL
Salicylic Acid	2.86 mg/dL
Theophylline	6 mg/dL

ADDITIONAL INFORMATION

For a patient/user/third party in the European Union and in countries with identical regulatory regime (Regulation 2017/746/EU on In vitro Diagnostic Medical Devices); if, during the use of this device or as a result of its use, a serious incident has occurred, please report it to the manufacturer and/or its authorized representative and to your national authority.

Notice to User

Any serious incident that has occurred in relation to this device should be reported to Beckman Coulter and the competent authority of the Member State in which the user and/or patient is established.

SHIPPING DAMAGE

If damaged product is received, notify your Beckman Coulter Clinical Support Center.

REVISION HISTORY

Removed Equipment and Materials Section

Updated AU to AU/DxC AU throughout

Updated Testing Procedure point 1

Updated results interpretation section

Updated Performance Characteristics section

Preceding version revision history

Revised Reagent Storage and Stability section.

Updated Performance Characteristics section

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