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ACCESS
Immunoassay Systems

Instructions For Use

ACCESS SENSITIVE ESTRADIOL
Estradiol

REF B84493

FOR PROFESSIONAL USE ONLY

Rx Only

FOR USE ON ACCESS IMMUNOASSAY SYSTEMS WITH TEST NAME: SNSE2

ANNUAL REVIEW

Reviewed by	Date	Reviewed by	Date

PRINCIPLE

INTENDED USE

The Access Sensitive Estradiol assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of estradiol levels in human serum and plasma using the Access Immunoassay Systems.

SUMMARY AND EXPLANATION

Estradiol (17β-estradiol) is a natural estrogen with a molecular mass of 272.4 daltons.[1] Most circulating estradiol is strongly bound to sex hormone binding protein and loosely bound to albumin. It is estimated that only 1-5% of estradiol is free (unbound).[2] In non-pregnant women, estradiol is secreted by the ovary and the corpus luteum. The adrenals and testes (in men) are also believed to secrete minute amounts of estradiol.[3]

Estradiol levels are lowest at menses and into the early follicular phase and rise in the late follicular phase to a peak just prior to the hLH (human Luteinizing Hormone) surge, initiating ovulation. As the hLH peaks, the levels of estradiol decrease before rising again in the luteal phase. Endometrial growth is stimulated by estradiol and progesterone (secreted by the corpus luteum) in preparation for implantation of a fertilized egg. If conception does not occur, the secretion of estradiol and progesterone by the corpus luteum decreases, initiating menses.[4,5]

Levels of estradiol are used to monitor ovulatory status.[2] Because estradiol levels reflect follicular maturation, the measurement of estradiol as cited in the scientific literature has been used as a valuable tool in the assessment of sexual development in children, anovulation and/or amenorrhea, polycystic ovary syndrome and causes of infertility and menopause.[3,4,6]

During in vitro fertilization, estradiol levels are routinely measured after gonadotropin stimulation to determine follicular status.[7] Estradiol also affects areas other than reproductive tissues such as cardiovascular, immune and central nervous systems.[8] For this reason estrogen has been investigated in the pathogenesis of cardiovascular disease,

hormone-dependent cancers and osteoporotic fracture.[9] Abnormally high levels in males are indicative of feminizing syndromes such as gynecomastia.[10]

METHODOLOGY

The Access Sensitive Estradiol assay is a competitive binding immunoenzymatic assay. A sample is added to a reaction vessel with displacer and an anti-estradiol conjugate (anti-estradiol sheep monoclonal antibody conjugated to alkaline phosphatase in a MES-buffered protein solution). After incubation paramagnetic particles coated with estradiol analog are added. Estradiol in the sample competes with the estradiol analog on the paramagnetic particles for binding sites on a limited amount of specific anti-estradiol conjugate. The resulting estradiol analog-antibody complexes are bound on the solid phase.

After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is inversely proportional to the concentration of estradiol in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

SPECIMEN

SPECIMEN STORAGE AND STABILITY

Specimen	Type	Room Temperature (hours)	2°C to 8°C (days)
Serum	Gel, No gel	8	7
Plasma	Lithium heparin, Sodium heparin, EDTA	8	7

SPECIMEN COLLECTION AND PREPARATION

1. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[11,12] To minimize the effect of preanalytical factors observe the following recommendations for handling and processing blood samples:[11]
   A. Collect all blood samples observing routine precautions for venipuncture.
      a. Follow blood collection tube manufacturer's recommendations for centrifugation.
      b. Ensure residual fibrin and cellular matter has been removed prior to analysis.
   B. Allow serum samples to clot completely before centrifugation in a vertical, closure-up position.
      a. Nonanticoagulated tubes containing gel separator should be stored in an upright position as soon as the mixing is complete.
      b. Precentrifugation serum/cells contact time is according to tube manufacturer's recommendations. Clotting may be slowed at cooler temperatures or if patient is on anticoagulant therapy.
2. Each laboratory should determine the acceptability of its own blood collection tubes and separation products. Variations in these products may exist between manufacturers and, at times, from lot-to-lot.
3. Alternate collection types may be appropriate if the laboratory has established its own performance characteristics as defined by applicable law.

4. Avoid assaying lipemic or hemolyzed samples.
5. Thaw samples no more than three times.
6. If the assay will not be completed within 7 days, freeze at -20°C or colder.

REAGENTS

CONTENTS

Access Sensitive Estradiol Reagent Pack

Cat. No. B84493: 100 determinations, 2 packs, 50 tests/pack

Well	Ingredients
R1a:	Dynabeads* paramagnetic particles coated with streptavidin, biotin and estradiol analog coupled to biotin in a Tris buffer with proteins (fish), surfactant and 0.0125% Cosmocil CQ**.
R1b:	Tris buffer with proteins (goat, bovine), surfactant, < 0.1% azide and 0.1% Proclin 300***.
R1c:	Sheep monoclonal anti estradiol alkaline phosphatase conjugate in a MES buffer with proteins (goat, avian), surfactant, < 0.1% azide and 0.1% Proclin 300.

*Dynabeads is a registered trademark of Dynal A.S., Oslo, Norway.

**Cosmocil is a trademark of Arch Chemicals, Inc.

***ProClin™ is a trademark of The Dow Chemical Company (“Dow”) or an affiliated company of Dow.

WARNING AND PRECAUTIONS

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- For hazards presented by the product refer to the following sections: REACTIVE INGREDIENTS and GHS HAZARD CLASSIFICATION.

REACTIVE INGREDIENTS

⚠ 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

Estradiol Dissociation buffer pH=7.6 (Compartment R1b)	WARNING	
		
	H316	Causes mild skin irritation.
	H317	May cause an allergic skin reaction.
	P280	Wear protective gloves, protective clothing and eye/face protection.
	P332+P313	If skin irritation occurs: Get medical advice/attention.
	P333+P313	If skin irritation or rash occurs: Get medical advice/attention.
	P362+P364	Take off contaminated clothing and wash it before use.
		Tris(hydroxymethyl)– aminomethane 1 - 5%
		reaction mass of: 5-chloro-2-methyl-4-isothiazolin -3-one [EC# 247-500-7] and 2-methyl-4-isothiazolin-3-one [EC# 220-239-6](3:1) < 0.05%
W.S. Anti-Estradiol Conjugate coupled to rec-ALP (Compartment R1c)	WARNING	
		
	H317	May cause an allergic skin reaction.
	P280	Wear protective gloves, protective clothing and eye/face protection.
	P333+P313	If skin irritation or rash occurs: Get medical advice/attention.
	P362+P364	Take off contaminated clothing and wash it before use.
		reaction mass of: 5-chloro-2-methyl-4-isothiazolin -3-one [EC# 247-500-7] and 2-methyl-4-isothiazolin-3-one [EC# 220-239-6](3:1) < 0.05%

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

MATERIALS NEEDED BUT NOT SUPPLIED WITH REAGENT KIT

1. Access Sensitive Estradiol Calibrators
   Provided at zero and approximately 11.0, 32.0, 292, 885 and 5,200 pg/mL (0, 40.4, 117, 1,072, 3,249 and 19,089 pmol/L).
   Cat. No. B84494
2. Quality Control (QC) materials: commercial control material.
3. Access Sensitive Estradiol Calibrator S0

Cat. No. B97145

4. Access Sample Diluent A
   Diluent Pack Cat. No. A79783 (For use with the UniCel DxI system onboard dilution feature.)
5. Access Substrate
   Cat. No. 81906
6. Access 2 Immunoassay Systems:
   Access Wash Buffer II, Cat. No. A16792
7. UniCel DxI Immunoassay Systems:
   UniCel DxI Wash Buffer II, Cat. No. A16793

REAGENT PREPARATION

Provided ready to use.

REAGENT STORAGE AND STABILITY

Stability	
Unopened at 2°C to 10°C	Up to stated expiration date
After opening at 2°C to 10°C	28 days

- Store upright.
- Refrigerate at 2°C to 10°C for a minimum of two hours before use on the instrument.
- Signs of possible deterioration are a broken elastomeric layer on the pack or quality control values out of range.
- If the reagent pack is damaged (e.g., a broken elastomer), discard the pack.
- Discard reagents if any discoloration is observed.
- Do not freeze

CALIBRATION

CALIBRATION INFORMATION

An active calibration curve is required for all tests. For the Access Sensitive Estradiol assay, calibration is required every 28 days. See calibrator Instructions For Use (IFU) for additional calibration information. 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.

QUALITY CONTROL

Quality control materials simulate the characteristics of samples and are essential for monitoring the system performance of immunochemical assays. Because samples can be processed at any time in a “random access” format rather than a “batch” format, quality control materials should be included in each 24-hour time period.[13] Include commercially available quality control materials that cover at least two levels of analyte.

TESTING PROCEDURE(S)

PROCEDURE

1. 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, calibration procedures, operational limitations and precautions, hazards, maintenance, and troubleshooting.

   A. The system default unit of measure for sample results is pg/mL. To change sample reporting units to the International System of Units (SI units), pmol/L, refer to the appropriate system manuals and/or Help system. To manually convert concentrations to the International System, multiply pg/mL by multiplication factor 3.671.

2. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.

3. Use thirty (30) µL of sample for each determination in addition to the sample container and system dead volumes when requesting the Access Sensitive Estradiol assay. Use one hundred and fifty-five (155) µL of sample in addition to the sample container and system dead volumes for each determination run with the DxI system onboard dilution feature (test name: dSNE2). Refer to the appropriate system manuals and/or Help system for the minimum sample volume required.

4. Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.

   A. Select SNSE2 as the test name for assaying samples containing estradiol concentrations up to the concentration of the Access Sensitive Estradiol S5 calibrator.

   B. UniCel DxI users may use the UniCel DxI onboard dilution feature (test name: dSNE2) for assaying samples containing estradiol concentrations greater than the Access Sensitive Estradiol S5 calibrator.

LIMITATIONS

1. 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.[14,15] Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.

2. Other potential interferences in the patient sample could be present and may cause erroneous results in immunoassays. Some examples that have been documented in literature include rheumatoid factor, endogenous alkaline phosphatase, fibrin, and proteins capable of binding to alkaline phosphatase.[16] Carefully evaluate results if the sample is suspected of having these types of interferences.

3. The Sensitive Estradiol 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.

RESULTS INTERPRETATION

Test results are determined automatically by the system software. The amount of analyte in the sample is determined from the measured light production by means of the stored calibration data. Test results can be reviewed using the appropriate screen. Refer to the appropriate system manuals and/or Help system for complete instructions on reviewing sample results.

REPORTING RESULTS

Samples can be accurately measured within the analytical range of the lower limit of detection and the highest calibrator value (approximately 15.0 - 5,200 pg/mL [55.1 - 19,089 pmol/L]).

- If a sample contains less than the lower limit of detection (LoD) for the assay, report the result as less than that value (i.e. < 15.0 pg/mL [55.1 pmol/L]). When the DxI system onboard dilution feature is used, the system will report results as less than 3,400 pg/mL (12,481 pmol/L).
- If a sample contains more than the stated value of the highest Access Sensitive Estradiol Calibrator (S5), report the result as greater than that value (i.e., > 5,200 pg/mL [> 19,089 pmol/L]). Alternatively, dilute one volume of sample with one volume of Access Sensitive Estradiol Calibrator S0.

Refer to the appropriate system manuals and/or Help system for instructions on entering a sample dilution in a test request. The system reports the results adjusted for the dilution.

Onboard Dilution Feature for use on UniCel DxI systems:

The DxI system onboard dilution feature automates the dilution process, using one volume of sample with one volume of Access Sample Diluent A, allowing samples to be quantitated up to approximately 10,400 pg/mL [38,178 pmol/L]. The system reports the results adjusted for the dilution.

EXPECTED RESULTS

1. Each laboratory should determine its own reference intervals appropriate to the laboratory's patient population; including age of the patient.
2. Estradiol concentrations were measured in human serum samples from apparently healthy adult male, female and pediatric subjects. Adult female subjects were not currently pregnant, not using hormonally based birth control in the three months prior to study, not using hormonal therapy in the six months prior to the study, had regular menstrual cycles (cycled females) and no previous history of ovarian surgery. Post-menopausal women were not on hormone replacement therapy. Pediatric age ranges were partitioned based on a reference by Karbasy, et. al.[17] Serum samples were analyzed using multiple Access Immunoassay Systems with the Access Sensitive Estradiol assay following the CLSI EP28-A3c guideline.[18] The observed ranges of estradiol concentrations are shown below for each population represented:

Non-pregnant females	Range of days from hLH peak (day 0)	N	Median (pg/mL)	Lower 2.5th Percentile Limit: (95% CI) pg/mL	Upper 97.5th Percentile Limit: (95% CI) pg/mL
Early Follicular	-14 to -10	49	36.9	22.4 (20.0-25.1)	115 (83.9-157)
Mid Follicular	-9 to -4	49	53.0	25.0 (20.7-30.1)	115 (95.5-139)
Ovulatory Peak	0	50	202	32.1 (19.3-53.5)	517 (429-622)
Mid Luteal	+4 to +11	50	127	36.5 (25.8-51.8)	246 (217-279)

Post-Menopausal Females	N	Median (pg/mL)	Upper 95th Percentile Limit: (95% CI) pg/mL
Not on hormone therapy	160	< 15.0	25.1 (19.9-30.0)

One-sided test is used due to skewed data distribution. Normal reference interval is defined as the values ≤ upper 95th percentile limit.

Males	N	Median (pg/mL)	Lower 2.5th Percentile Limit pg/mL	Upper 97.5th Percentile Limit: (95% CI) pg/mL
≥ 19 years old	129	22.2	< 15.0	31.5 (29.8-33.1)

Pediatric	Age Range (years)	N	Median (pg/mL)	Upper 95th Percentile Limit: (95% CI) pg/mL
Pediatric (male and female)	0 to < 1	114	< 15.0	38.2 (32.6-43.7)
Pre-puberty female	1 to < 12	117	< 15.0	16.0 (< 15.0-20.3)
Puberty female	12 to < 19	150	36.5	196 (162-230)
Pre-puberty male	1 to < 12	99	< 15.0	< 15.0
Puberty male	12 to < 19	58	19.5	34.8 (30.8-38.7)

One-sided test is used due to skewed data distribution. Normal reference interval is defined as the values ≤ upper 95th percentile limit.

PERFORMANCE CHARACTERISTICS

PERFORMANCE CHARACTERISTICS

Representative data is provided for illustration only. Performance obtained in individual laboratories may vary.

METHODS COMPARISON

A comparison of 135 values using the Access Sensitive Estradiol assay on an Access Immunoassay System and mass spectrometry including comparison to the ID/GC/MS reference measurement procedure (RMP) developed at Ghent University and an LC-MS tandem method gave the following statistical data using Passing-Bablok regression and Pearson's correlation based on the CLSI EP09-A3 guideline:[19]

N	Range of Observations (pg/mL)	Intercept (pg/mL) [95% CI]	Slope [95% CI]	Correlation Coefficient (r)
135 (combined GC-MS and LC-MS)	15.7 to 4,838	-2.957 [-8.46 to 0.63]	0.98 [0.95 to 1.00]	0.99
48 (GC-MS only)	15.7 to 4,838	3.224 [-0.44 to 8.10]	0.99 [0.97 to 1.03]	0.99
87 (LC-MS only)	17.3 to 2,119	-5.121 [-14.35 to 2.95]	0.91 [0.83 to 1.04]	0.97

LINEARITY

The Access Sensitive Estradiol assay demonstrated acceptable linearity throughout the analytical measuring range of 15.0 pg/mL (55.1 pmol/L) to approximately 5,200 pg/mL (19,089 pmol/L). Based on CLSI EP06-A[20], one high sample [approximately 5,200 pg/mL and one low sample [approximately 8.8 pg/mL] were mixed to make 9 sample concentrations evenly distributed across the analytical measuring range. Four replicates of the 7 mixed samples, 8 replicates of the low sample and 4 replicates of the high sample were tested on multiple Access Immunoassay Systems.

IMPRECISION

The Access Sensitive Estradiol assay exhibits within laboratory (total) imprecision ≤ 10% at concentrations greater than 30.0 pg/mL (110.1 pmol/L), and within laboratory (total) standard deviation (SD) ≤ 5.00 pg/mL (18.36 pmol/L) at ≤ 30.0 pg/mL (110.1 pmol/L).

One study, using six serum-based samples on one Access Immunoassay System generating a total of 40 assays, two replicates per assay, over 10 days with 4 runs per day provided the following data, calculated based on CLSI EP05-A3[21] guidelines.

			Within-Run		Between-Run		Between-Day		Within Lab (Total Imprecision)	
Sample	N	Grand Mean (n=40) (pg/mL)	SD (pg/mL)	CV (%)	SD (pg/mL)	CV (%)	SD (pg/mL)	CV (%)	SD (pg/mL)	CV (%)
Sample 1	82	23.3	2.50	NA	2.16	NA	1.13	NA	3.49	NA
Sample 2	84	41.7	2.00	5%	1.75	4%	1.16	3%	2.90	7%
Sample 3	84	173	3.23	2%	2.95	2%	3.11	2%	5.36	3%
Sample 4	84	799	13.62	2%	18.96	2%	6.05	1%	24.11	3%
Sample 5	84	1,608	35.26	2%	35.89	2%	25.31	2%	56.32	4%
Sample 6	84	3,477	168.34	5%	225.36	6%	99.55	3%	298.39	9%

INTERFERING SUBSTANCES

Serum samples containing estradiol concentrations of 150 and 500 pg/mL were spiked with multiple concentrations of the substances below and run on multiple Access Immunoassay Systems. Values were calculated as described in CLSI EP07-A2[22]. Interference was determined by testing controls (no interfering substance added) and matched test samples (with interfering substance added). Of the compounds tested, none were found to cause significant interference (as defined by a shift in dose greater than 10%) using the highest test concentrations indicated in the table below.

Substance	High Concentration
Acetaminophen	20 mg/dL
Acetylsalicylic acid	65 mg/dL
Ascorbic acid	342 µmol/L

Substance	High Concentration
Bilirubin (conjugated)	43 mg/dL
Bilirubin (unconjugated)	40 mg/dL
Biotin	200 ng/mL
Fulvestrant	25,000 pg/mL
Hemoglobin	300 mg/dL
Heparin	3,000 U/L
2-hydroxy-Ibuprofen	50 mg/dL
Multi Vitamin (Centrum liquid)	0.38% (v/v)
Tamoxifen	4 µmol/L
Triglyceride (Triolein)	37 mmol/L
Total Protein	12 g/dL
Uric Acid	1.4 mmol/L

CROSS REACTIVITY

A study was performed to evaluate the potential cross-reactivity of the assay with other substances that are similar in structure to estradiol. Serum samples containing estradiol concentrations of approximately 150 and 500 pg/mL were spiked with multiple concentrations of the substances below and run on multiple Access Immunoassay Systems. Values were calculated as described in CLSI EP07-A2[22]. The percent cross-reactivity observed for the following substances is indicated below.

Substance	Highest Concentration Tested (µg/mL)	Highest Cross-Reactivity Observed (%)	Criteria (%) ≤
Aldosterone	100	0.000030	0.90
Androstenediol	53.7	0.0030	1.40
Androstenedione	50	0.000020	0.50
Estradiol valerate	0.7	0.40	1.00
17α-Estradiol	2	0.0040	1.00
17β-estradiol 3 glucuronide	0.3	0.10	1.00
3.17β-Estradiol diglucuronide	56.3	0.0030	1.00
Estriol	4.2	0.050	1.00
Estriol-3-sulfate	3.7	0.00030	1.00
Estriol-17-sulfate	0.3	0.00200	1.00
Estrone	0.4	0.40	2.0
Estrone-3-glucuronide	100	0.0020	1.00
Estrone-3-Sulfate	14.1	0.0010	1.70
Ethinyl estradiol	2.5	0.030	1.0

Substance	Highest Concentration Tested (µg/mL)	Highest Cross-Reactivity Observed (%)	Criteria (%) ≤
Norgestrel	100	0.000070	0.40
Testosterone	34.2	0.00060	0.21

ANALYTICAL SENSITIVITY

Parameter	Total Samples	Total Replicates Tested Per Study	Total Runs Per Study	Range of Observed Results	Criteria
Limit of Blank (LoB) (highest measurement result that is likely to be observed in a blank sample)	4	120	3	5.0-7.5 pg/mL (18.5-27.6 pmol/L)	≤ 10.0 pg/mL (≤ 36.7 pmol/L)
Limit of Detection (LoD) (lowest concentration of analyte that can be consistently detected)	5	225	5	9.4-12.4 pg/mL (34.5-45.4 pmol/L)	≤ 15.0 pg/mL (≤ 55.1 pmol/L)
Limit of Quantitation (LoQ) ≤ 20% within lab (total) CV	11	495	5	10.4-15.1 pg/mL (38.3-55.5 pmol/L)	≤ 19.0 pg/mL (≤ 69.7 pmol/L)

Per the study design the results were calculated using a protocol based on CLSI EP17-A2[23] with three reagent lots and one calibrator lot on multiple Access Immunoassay Systems for a total of six studies.

ADDITIONAL INFORMATION

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SYMBOLS KEY

Glossary of Symbols is available at techdocs.beckmancoulter.com (document number C02724)

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