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# Estradiol III

cobas®

**Estradiol - E2**

| REF | Σ | SYSTEM |
|---|---|---|
| | | Elecsys 2010 |
| | | MODULAR ANALYTICS E170 |
| **06656021** 190 | 100 | **cobas e** 411 |
| | | **cobas e** 601 |
| | | **cobas e** 602 |

For USA: Elecsys Estradiol III Assay

## English

### Intended use

Immunoassay for the in vitro quantitative determination of estradiol in human serum and plasma.

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on Elecsys and **cobas e** immunoassay analyzers.

### Summary

Estrogens are responsible for the development of the secondary female sex characteristics. Together with gestagens they control all the important female reproductive processes.

The biologically most active estrogen is 17β-estradiol. This is a steroid hormone having a molecular weight of 272 daltons.

Estrogens are produced primarily in the ovary (follicle, corpus luteum), but small quantities are also formed in the testes and in the adrenal cortex. During pregnancy, estrogens are mainly formed in the placenta. About 98 % of estradiol is bound to transport proteins (SHBG = sex hormone binding globulin).[1]

Estrogen secretion is biphasic during the menstrual cycle. The determination of estradiol is utilized clinically in the elucidation of fertility disorders in the hypothalamus-pituitary-gonad axis, gynecomastia, estrogen-producing ovarian and testicular tumors and in hyperplasia of the adrenal cortex. Further clinical indications are the monitoring of fertility therapy and determining the time of ovulation within the framework of in vitro fertilization (IVF).[2,3,4]

The Elecsys Estradiol III assay employs a competitive test principle using two monoclonal antibodies specifically directed against 17β-estradiol. Endogenous estradiol released from the sample by mesterolone competes with the added estradiol derivative labeled with a ruthenium complex[a)] for the binding sites on the biotinylated antibody.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex ($Ru(bpy)_3^{2+}$)

### Test principle

Competition principle. Total duration of assay: 18 minutes.

- 1st incubation: By incubating the sample (25 µL) with two estradiol-specific biotinylated antibodies, immunocomplexes are formed, the amount of which is dependent upon the analyte concentration in the sample.
- 2nd incubation: After addition of streptavidin-coated microparticles and an estradiol derivative labeled with a ruthenium complex, the still-vacant sites of the biotinylated antibodies become occupied, with formation of an antibody-hapten complex. The entire complex becomes bound to the solid phase via interaction of biotin and streptavidin.
- The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell/ProCell M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the reagent barcode.

### Reagents - working solutions

The reagent rackpack is labeled as E2 III.

M Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL:

Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-estradiol-Ab~biotin (gray cap), 1 bottle, 9 mL:

Two biotinylated monoclonal anti-estradiol antibodies (rabbit) 2.5 ng/mL and 4.5 ng/mL; mesterolone 130 ng/mL; MES[b)] buffer 50 mmol/L, pH 6.0; preservative.

R2 Estradiol-peptide~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 9 mL:

Estradiol derivative, labeled with ruthenium complex 4.5 ng/mL; MES buffer 50 mmol/L, pH 6.0; preservative.

b) MES = 2-morpholino-ethane sulfonic acid

### Precautions and warnings

For in vitro diagnostic use.
Exercise the normal precautions required for handling all laboratory reagents.
Disposal of all waste material should be in accordance with local guidelines.
Safety data sheet available for professional user on request.

For USA: For prescription use only.

Avoid foam formation in all reagents and sample types (specimens, calibrators and controls).

### Reagent handling

The reagents in the kit have been assembled into a ready-for-use unit that cannot be separated.

All information required for correct operation is read in from the respective reagent barcodes.

### Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the Elecsys reagent kit **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

| Stability: | |
|---|---|
| unopened at 2-8 °C | up to the stated expiration date |
| after opening at 2-8 °C | 12 weeks |
| on the analyzers | 8 weeks |

### Specimen collection and preparation

Only the specimens listed below were tested and found acceptable.

Serum collected using standard sampling tubes or tubes containing separating gel.

Li-heparin, $K_2$-EDTA and $K_3$-EDTA plasma as well as plasma separation tubes.

Criterion: Slope 0.9-1.1 + intercept within < ± 10 pg/mL + coefficient of correlation ≥ 0.95.

For individual samples recovery within 70-130 % of serum value > 100 pg/mL, recovery of ± 20 pg/mL of serum value ≤ 100 pg/mL.

Stable for 12 hours at 20-25 °C, 2 days at 2-8 °C, 6 months at -20 °C. Freeze only once.

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

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Centrifuge samples containing precipitates and frozen samples before performing the assay.

Do not use heat-inactivated samples.

Do not use samples and controls stabilized with azide.

Ensure the samples, calibrators and controls are at 20-25 °C prior to measurement.

Due to possible evaporation effects, samples, calibrators and controls on the analyzers should be analyzed/measured within 2 hours.

**Materials provided**

See "Reagents – working solutions" section for reagents.

**Materials required (but not provided)**

- REF 06656048190, Estradiol III CalSet, for 4 x 1 mL
- REF 11731416190, PreciControl Universal, for 2 x 3 mL each of PreciControl Universal 1 and 2
- REF 11731416160, PreciControl Universal, for 2 x 3 mL each of PreciControl Universal 1 and 2 (for USA)
- REF 03609987190, Diluent MultiAssay, 2 x 16 mL sample diluent
- General laboratory equipment
- Elecsys 2010, MODULAR ANALYTICS E170 or **cobas e** analyzer

Accessories for Elecsys 2010 and **cobas e** 411 analyzers:

- REF 11662988122, ProCell, 6 x 380 mL system buffer
- REF 11662970122, CleanCell, 6 x 380 mL measuring cell cleaning solution
- REF 11930346122, Elecsys SysWash, 1 x 500 mL washwater additive
- REF 11933159001, Adapter for SysClean
- REF 11706802001, Elecsys 2010 AssayCup, 60 x 60 reaction vessels
- REF 11706799001, Elecsys 2010 AssayTip, 30 x 120 pipette tips

Accessories for MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers:

- REF 04880340190, ProCell M, 2 x 2 L system buffer
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- REF 03023141001, PC/CC-Cups, 12 cups to prewarm ProCell M and CleanCell M before use
- REF 03005712190, ProbeWash M, 12 x 70 mL cleaning solution for run finalization and rinsing during reagent change
- REF 03004899190, PreClean M, 5 x 600 mL detection cleaning solution
- REF 12102137001, AssayTip/AssayCup Combimagazine M, 48 magazines x 84 reaction vessels or pipette tips, waste bags
- REF 03023150001, WasteLiner, waste bags
- REF 03027651001, SysClean Adapter M

Accessories for all analyzers:

- REF 11298500316, ISE Cleaning Solution/Elecsys SysClean, 5 x 100 mL system cleaning solution
- REF 11298500160, ISE Cleaning Solution/Elecsys SysClean, 5 x 100 mL system cleaning solution (for USA)

**Assay**

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator's manual for analyzer-specific assay instructions.

Resuspension of the microparticles takes place automatically prior to use. Read in the test-specific parameters via the reagent barcode. If in exceptional cases the barcode cannot be read, enter the 15-digit sequence of numbers.

MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers: PreClean M solution is necessary.

Bring the cooled reagents to approximately 20 °C and place on the reagent disk (20 °C) of the analyzer. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the bottles.

**Calibration**

Traceability: This method has been standardized against CRM 6004a via ID-GC/MS (isotope dilution-gas chromatography/mass spectrometry).[5]

Every Elecsys reagent set has a barcoded label containing specific information for calibration of the particular reagent lot. The predefined master curve is adapted to the analyzer using the relevant CalSet.

*Calibration frequency:* Calibration must be performed once per reagent lot using fresh reagent (i.e. not more than 24 hours since the reagent kit was registered on the analyzer). Renewed calibration is recommended as follows:

- after 1 month (28 days) when using the same reagent lot
- after 7 days (when using the same reagent kit on the analyzer)
- as required: e.g. quality control findings outside the defined limits

**Quality control**

For quality control, use PreciControl Universal.

In addition, other suitable control material can be used.

Controls for the various concentration ranges should be run individually at least once every 24 hours when the test is in use, once per reagent kit, and following each calibration.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

Follow the applicable government regulations and local guidelines for quality control.

**Calculation**

The analyzer automatically calculates the analyte concentration of each sample (either in pmol/L, pg/mL, ng/L or additionally in nmol/L with MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers).

| | |
|---|---|
| Conversion factors: | pmol/L x 0.272 = pg/mL (ng/L) |
| | pg/mL x 3.67 = pmol/L |
| | pg/mL x 0.00367 = nmol/L |

**Limitations - interference**

The assay is unaffected by icterus (bilirubin ≤ 1129 µmol/L or ≤ 66 mg/dL), hemolysis (Hb ≤ 0.621 mmol/L or ≤ 1.0 g/dL), lipemia (Intralipid ≤ 1000 mg/dL) and biotin (≤ 147 nmol/L or ≤ 36 ng/mL).

Criterion: Recovery within ± 10 % of initial value.

Samples should not be taken from patients receiving therapy with high biotin doses (i.e. > 5 mg/day) until at least 8 hours following the last biotin administration.

No interference was observed from rheumatoid factors up to a concentration of 1200 IU/mL.

In vitro tests were performed on 17 commonly used pharmaceuticals. No interference with the assay was found.

Erroneous test results may be obtained from samples taken from patients who have been exposed to vaccines containing rabbit serum or when keeping rabbits as pet animals.

In rare cases, interference due to extremely high titers of antibodies to analyte-specific antibodies, streptavidin or ruthenium can occur. These effects are minimized by suitable test design.

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

**Limits and ranges**

**Measuring range**

18.4-11010 pmol/L (5-3000 pg/mL) (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 18.4 pmol/L or < 5 pg/mL. Values above the measuring range are reported as > 11010 pmol/L or > 3000 pg/mL (or up to 110100 pmol/L or 30000 pg/mL for 10-fold diluted samples).

**Lower limits of measurement**

*Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ)*

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Limit of Blank = 11 pmol/L (3 pg/mL)

Limit of Detection = 18.4 pmol/L (5 pg/mL)

Limit of Quantitation = 91.8 pmol/L (25 pg/mL) with a total allowable error of ≤ 30 %

A study was performed for LoQ using human serum samples diluted and measured in 6 runs over ≥ 3 days on 2 analyzers. At a total allowable error of ≤ 30 % LoQ was 61.3 pmol/L (16.7 pg/mL).

The Limit of Blank, Limit of Detection and Limit of Quantitation were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A requirements.

The Limit of Blank is the 95$^{th}$ percentile value from n ≥ 60 measurements of analyte-free samples over several independent series. The Limit of Blank corresponds to the concentration below which analyte-free samples are found with a probability of 95 %.

The Limit of Detection is determined based on the Limit of Blank and the standard deviation of low concentration samples. The Limit of Detection corresponds to the lowest analyte concentration which can be detected (value above the Limit of Blank with a probability of 95 %).

The Limit of Quantitation is defined as the lowest amount of analyte in a sample that can be accurately quantitated with a total allowable error of ≤ 30 %.

### Dilution

Samples with estradiol concentrations above the measuring range can be diluted with Diluent MultiAssay. The recommended dilution is 1:10 (automatically by the MODULAR ANALYTICS E170, Elecsys 2010 or **cobas e** analyzers). The concentration of the diluted sample must be > 881 pmol/L (> 240 pg/mL).

After dilution by the analyzers, the MODULAR ANALYTICS E170, Elecsys 2010 and **cobas e** software automatically takes the dilution into account when calculating the sample concentration.

The endogenous analyte concentration of the diluent (< 220 pmol/L or < 60.0 pg/mL) is not taken into account for dilutions above the measuring range.

### Expected values

The reference ranges were determined in a Caucasian population.

| Test subjects | N | 2.5th percentile pmol/L (90 % CI*) | Median pmol/L (90 % CI) | 97.5th percentile pmol/L (90 % CI) |
|---|---|---|---|---|
| Healthy men | 146 | 94.8 (57.0-97.5) | 133 (129-135) | 223 (194-232) |
| Healthy women | | | | |
| • Follicular phase | 146 | 45.4 (22.8-61.2) | 196 (183-213) | 854 (633-1154) |
| • Ovulation phase | 150 | 151 (105-158) | 462 (416-533) | 1461 (1162-1925) |
| • Luteal phase | 151 | 81.9 (28.2-127) | 370 (335-419) | 1251 (1077-2759) |
| • Postmenopause | 142 | < 18.4 (< 18.4-< 18.4) | <18.4 (< 18.4-19.2) | 505 (189-1150) |
| Healthy pregnant women | | | | |
| • 1st trimester | 136 | 563 (467-636) | 3133 (2703-4004) | 11902 (9891-15271) |
| • 2nd trimester | 140 | 5729 (4173-7457) | 28402 (24207-32090) | 78098 (69143-92227) |
| • 3rd trimester | 136 | 31287 (27151-34175) | 64684 (62353-68189) | > 110100 (107164-> 110100) |

* CI = confidence interval

| Test subjects | N | 2.5th percentile pg/mL (90 % CI) | Median pg/mL (90 % CI) | 97.5th percentile pg/mL (90 % CI) |
|---|---|---|---|---|
| Healthy men | 146 | 25.8 (15.5-26.5) | 36.1 (35.3-36.7) | 60.7 (52.9-63.3) |
| Healthy women | | | | |
| • Follicular phase | 146 | 12.4 (6.2-16.7) | 53.4 (49.8-58.1) | 233 (173-315) |
| • Ovulation phase | 150 | 41.0 (28.6-43.2) | 126 (113-145) | 398 (317-525) |
| • Luteal phase | 151 | 22.3 (7.69-34.6) | 101 (91.2-114) | 341 (294-752) |
| • Postmenopause | 142 | < 5 (< 5-< 5) | <5 (< 5-5.24) | 138 (51.6-314) |
| Healthy pregnant women | | | | |
| • 1st trimester | 136 | 154 (127-173) | 854 (737-1091) | 3243 (2695-4161) |
| • 2nd trimester | 140 | 1561 (1137-2032) | 7739 (6596-8744) | 21280 (18840-25130) |
| • 3rd trimester | 136 | 8525 (7398-9312) | 17625 (16990-18580) | > 30000 (29200-> 30000) |

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

### Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

### Precision

Precision was determined using Elecsys reagents, samples and controls in a protocol (EP5-A2) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day in duplication each for 21 days (n = 84). The following results were obtained:

| Elecsys 2010 and **cobas e** 411 analyzers | | | | | |
|---|---|---|---|---|---|
| | | **Repeatability** | | **Intermediate precision** | |
| Sample | Mean pmol/L | SD pmol/L | CV % | SD pmol/L | CV % |
| Human serum 1 | 93.3 | 7.91 | 8.5 | 11.1 | 11.9 |
| Human serum 2 | 166 | 7.75 | 4.7 | 11.4 | 6.8 |
| Human serum 3 | 605 | 18.8 | 3.1 | 20.4 | 3.4 |
| Human serum 4 | 5021 | 97.7 | 1.9 | 125 | 2.5 |
| Human serum 5 | 10760 | 253 | 2.4 | 297 | 2.8 |
| PC U[c)]1 | 316 | 11.0 | 3.5 | 14.1 | 4.5 |
| PC U2 | 1514 | 47.8 | 3.2 | 53.7 | 3.5 |

c) PC U = PreciControl Universal

| MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers | | | | | |
|---|---|---|---|---|---|
| | | **Repeatability** | | **Intermediate precision** | |
| Sample | Mean pmol/L | SD pmol/L | CV % | SD pmol/L | CV % |
| Human serum 1 | 101 | 6.79 | 6.7 | 10.6 | 10.6 |
| Human serum 2 | 173 | 6.46 | 3.7 | 9.8 | 5.7 |
| Human serum 3 | 584 | 9.62 | 1.6 | 14.4 | 2.5 |
| Human serum 4 | 4661 | 53.2 | 1.1 | 86.2 | 1.9 |

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**Estradiol - E2**

| MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers | | | | | |
|---|---|---|---|---|---|
| | | **Repeatability** | | **Intermediate precision** | |
| Sample | Mean pmol/L | SD pmol/L | CV % | SD pmol/L | CV % |
| Human serum 5 | 9982 | 189 | 1.9 | 295 | 3.0 |
| PC U1 | 329 | 7.82 | 2.4 | 12.4 | 3.8 |
| PC U2 | 1497 | 18.0 | 1.2 | 30.8 | 2.1 |

| Elecsys 2010 and **cobas e** 411 analyzers | | | | | |
|---|---|---|---|---|---|
| | | **Repeatability** | | **Intermediate precision** | |
| Sample | Mean pg/mL | SD pg/mL | CV % | SD pg/mL | CV % |
| Human serum 1 | 25.4 | 2.16 | 8.5 | 3.03 | 11.9 |
| Human serum 2 | 45.3 | 2.11 | 4.7 | 3.10 | 6.8 |
| Human serum 3 | 165 | 5.14 | 3.1 | 5.55 | 3.4 |
| Human serum 4 | 1368 | 26.6 | 1.9 | 34.1 | 2.5 |
| Human serum 5 | 2932 | 68.9 | 2.4 | 80.9 | 2.8 |
| PC U1 | 86.1 | 2.99 | 3.5 | 3.83 | 4.5 |
| PC U2 | 413 | 13.0 | 3.2 | 14.6 | 3.5 |

| MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers | | | | | |
|---|---|---|---|---|---|
| | | **Repeatability** | | **Intermediate precision** | |
| Sample | Mean pg/mL | SD pg/mL | CV % | SD pg/mL | CV % |
| Human serum 1 | 27.4 | 1.85 | 6.7 | 2.90 | 10.6 |
| Human serum 2 | 47.1 | 1.76 | 3.7 | 2.67 | 5.7 |
| Human serum 3 | 159 | 2.62 | 1.6 | 3.92 | 2.5 |
| Human serum 4 | 1270 | 14.5 | 1.1 | 23.5 | 1.9 |
| Human serum 5 | 2720 | 51.5 | 1.9 | 80.5 | 3.0 |
| PC U1 | 89.6 | 2.13 | 2.4 | 3.37 | 3.8 |
| PC U2 | 408 | 4.91 | 1.2 | 8.39 | 2.1 |

**Method comparison**

A comparison of the Elecsys Estradiol III assay (y) with ID-GC/MS (x) using clinical samples gave the following correlations (pg/mL):

Number of samples measured: 25

| Passing/Bablok[6] | Linear regression |
|---|---|
| y = 0.993x + 1.26 | y = 1.00x + 2.07 |
| τ = 0.987 | r = 0.999 |

The sample concentrations were between 37.4 and 10768 pmol/L (10.2 and 2934 pg/mL) (ID-GC-MS concentrations).

**Analytical specificity**

For the Estradiol III assay, the following cross-reactivities were found (in %):

*a) Substance added in a concentration of 0.001 µg/mL:*

| | |
|---|---|
| 6-alpha-Hydroxy-Estradiol | 74.1 |

*b) Substance added in a concentration of 0.01 µg/mL:*

| | |
|---|---|
| 4-Hydroxyestradiol | 0.754 |

*c) Substance added in a concentration of 0.1 µg/mL:*

| | |
|---|---|
| Aldosterone | 0.005 |
| Androstendione | 0.005 |
| Equiline | 0.057 |
| Estriol | 0.233 |
| Estrone | 0.757 |
| Estrone-3β-glucuronide | 0.003 |
| Estrone-3-sulfate | 0.002 |
| Ethisterone | 0.002 |
| Norethindrone acetate | n. d.[d)] |
| Pregnenolone | 0.007 |
| Progesterone | 0.004 |
| 2-Methoxyestradiol | 0.121 |
| 17β-Estradiol-3,17-sulfate | 0.002 |
| 17β-Estradiol-3-β-D-glucuronide | 0.008 |
| 17β-Estradiol-17-β-D-glucuronide | 0.001 |
| 17β-Estradiol-3-glucuronide-17-sulfate | n. d. |
| 17β-Estradiol-3-sulfate-17-glucuronide | 0.004 |
| 17β-Estradiol-3-sulfate | 0.009 |
| 17β-Estradiol-17-valerate | 0.163 |
| 17β-Estradiol-17-sulfate | 0.003 |
| 2-Hydroxyestradiol | 0.045 |
| 17-Hydroxyprogesterone | n. d. |

d) n. d. = not detectable

*d) Substance added in a concentration of 0.2 µg/mL:*

| | |
|---|---|
| 17-α-Ethinylestradiol | 0.334 |
| Cortisol | 0.003 |
| Cortisone | 0.001 |
| Tamoxifen | 0.001 |

*e) Substance added in a concentration of 0.25 µg/mL:*

| | |
|---|---|
| Chlomiphene | 0.001 |

*f) Substance added in a concentration of 1.0 µg/mL:*

| | |
|---|---|
| Prednisolone | n. d. |

*g) Substance added in a concentration of 10 µg/mL:*

| | |
|---|---|
| Danazol | 0.001 |
| DHEA-S | n. d. |
| Mesterolone | n. d. |
| Testosterone | n. d. |
| 5-α-Dihydrotestosterone (DHT) | n. d. |
| 5-Androstene-3β-,17β-diol | n. d. |

**References**


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For further information, please refer to the appropriate operator's manual for the analyzer concerned, the respective application sheets, the product information and the Method Sheets of all necessary components (if available in your country).

A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

**Symbols**

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard.

| | |
|---|---|
| CONTENT | Contents of kit |
| SYSTEM | Analyzers/Instruments on which reagents can be used |
| REAGENT | Reagent |
| CALIBRATOR | Calibrator |
| → | Volume after reconstitution or mixing |
| GTIN | Global Trade Item Number |

**FOR US CUSTOMERS ONLY: LIMITED WARRANTY**

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