Elecsys Anti-HEV IgM

cobas®

REF		Σ	SYSTEM
09056254190	09056254500	300	**cobas e** 402 **cobas e** 801

English

System information

Short name	ACN (application code number)
AHEVIGM	10223

Intended use

Immunoassay for the in vitro qualitative detection of IgM antibodies to the hepatitis E virus (HEV) in human serum and plasma. The Elecsys Anti-HEV IgM assay is used as an aid to detect an acute or recently acquired HEV infection.

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

Summary

HEV is the etiological agent of hepatitis E and is regarded as an emerging pathogen of global public health concern.[1,2] HEV infection is an important cause of both acute and chronic hepatitis, being responsible for more than 50 % of the cases of acute hepatitis in endemic countries.[3,4,5] A global burden of disease study estimated that HEV genotypes 1 and 2 account for approximately 20.1 million HEV infections, 3.4 million symptomatic cases, 70000 deaths, and 3000 stillbirths annually.[6,7]

HEV is an icosahedral, non-enveloped, positive-sense, single-stranded RNA virus with a diameter of 27-34 nm. The RNA genome of 7.2 kb has 3 open reading frames (ORFs): ORF1, encoding non-structural proteins involved in viral replication; ORF2, encoding a viral capsid protein important for virion assembly and immunogenicity; and ORF3, encoding a protein essential for virus release.[1,4,5,8,9,10,11]

HEV, which is classified as species Paslahepevirus balayani in the family Hepeviridae, genus Paslahepevirus, includes 8 genotypes, of which HEV 1-4 are the most frequently detected globally. HEV-1 and HEV-2 infect only humans, whereas HEV-3 and HEV-4 infect humans but also several animal species such as pig, boar, rabbit, and deer.[5,12,13,14,15,16,17] HEV-1 and HEV-2 are predominant in Africa and Asia,[1,12,18] while HEV-3 and HEV-4 are seen largely in the developed world.[1,12,18,19]

HEV-1 and HEV-2 are mainly transmitted by the fecal-oral route, principally via contaminated water, in areas of poor sanitation,[20] while HEV-3 and HEV-4 are transmitted zoonotically by direct contact with infected animals[1,8,20] or by consumption of contaminated food, primarily undercooked pork meat.[8,11,19,20] Vertical transmission from mother to fetus is one of the main transmission routes for HEV that causes premature birth and perinatal mortality.[21,22,23,24] In several countries, occasional transmission of HEV infection (HEV-3) through blood transfusion has been reported.[1,3,4]

HEV infection usually causes a mild or subclinical infection with a self-limiting illness that lasts from 2 to 6 weeks.[19,25] Symptomatic hepatitis E is similar to other acute hepatitis infections (non-specific prodromal symptoms of fatigue, nausea, vomiting as well as jaundice and elevated liver enzymes).[19] Testing for hepatitis E is recommended in all patients presenting with symptoms consistent with acute hepatitis, patients with unexplained flares of chronic hepatitis as well as in all immunocompromised patients with unexplained abnormal liver function tests.[11,26] An important differential diagnosis of acute hepatitis E is drug-induced liver injury.[26]

Mainly in immunocompromised patients, acute hepatitis can progress to chronic hepatitis (approximately 1-2 % of cases), cirrhosis, liver failure, and acute-on-chronic liver failure.[11,19,27,28] Pregnant women, particularly during the third trimester of pregnancy, are more vulnerable to HEV infections leading to severe clinical outcomes such as fulminant hepatic failure, birth complications, and a significant mortality rate as high as 10-30 %.[9,13,19,24,29,30] Therefore, antenatal screening for HEV antibodies should be considered.[31] Other high-risk populations are immunocompromised patients (especially transplant organ recipients), patients with underlying liver conditions, and elderly people.[4,5,9,29,30,32] Acute and chronic HEV infection have also been associated with extra-hepatic manifestations, especially neurological and renal disorders.[11,19,26,32] In the aforementioned clinical settings, it is imperative to test for HEV infection upon suspicion of viral hepatitis.[33,34]

Around 3 weeks post-infection, HEV RNA becomes detectable in blood and stool, with viremia lasting approximately 3-6 weeks, and shedding of virus in stool for approximately 4-6 weeks.[26] IgM antibodies against the HEV capsid protein are detectable in serum after 1-4 weeks for up to 6-9 months post-infection, and are a key marker of recent or current infection.[4,5,11,26,30,32,33] Anti-HEV IgG antibodies appear around the same time as or soon after anti-HEV IgM antibodies. They are an indicator of recent or past infection and usually persist for several years.[4,15,26,30,32,35]

Acute HEV infection can be diagnosed by the detection of anti-HEV antibodies (IgG, IgM, or both) in serum or plasma, in combination with testing for HEV RNA. Serological testing alone relies upon the combined detection of anti-HEV IgM and rising anti-HEV IgG titers.[26] Measuring rising anti-HEV IgG titers may help in diagnosis of HEV infection in situations with poor anti-HEV IgM response.[9] The presence of anti-HEV IgG determines past infection.[19,26,36,37] In addition, anti-HEV IgG testing is considered useful in seroprevalence studies. Moreover, in the future, testing for anti-HEV IgG titers may become useful for determining the effectiveness of HEV vaccines.[1]

Acute HEV infection does not usually require antiviral therapy.[26,38] Supportive care is the mainstay of treatment.[39] However, hospitalization is required for people with fulminant hepatitis and should also be considered for symptomatic pregnant women,[20,38] and ribavirin treatment may be considered in cases of severe acute hepatitis E, acute-on-chronic liver failure, or immunocompromised patients with chronic hepatitis E.[20,26] In certain situations, interferon or a reduction of immunosuppressive therapy have also been used successfully.[20,26]

The Elecsys Anti-HEV IgM assay uses recombinant proteins based on structural domains of HEV ORF2 (genotype 1 and 3) as antigens in a µ-capture assay format for the qualitative detection of IgM antibodies to HEV. Qualitative measurement of IgM antibodies to HEV is intended as an aid in the diagnosis of acute HEV infection by detecting anti-HEV IgM antibodies during acute infection, in combination with the detection of rising titers of IgG antibodies to HEV or HEV RNA and in conjunction with other laboratory results and clinical information, as part of the differential diagnosis of acute hepatitis to enable timely initiation of medical interventions. Testing for HEV infection, including anti-HEV IgM antibodies, is also indicated in pregnant women.

The Elecsys Anti-HEV IgM assay is not intended for use as a first-line screening test for donors of blood or blood products or human cells, tissues, and cellular and tissue-based products (HCT/Ps).

Test principle

µ-Capture test principle. Total duration of assay: 18 minutes.

- 1st incubation: 6 µL of sample are automatically prediluted 1:20 with Diluent Universal. Hepatitis E-specific recombinant antigen labeled with a ruthenium complex[a)] is added. Anti-HEV IgM antibodies present in the sample bind to the ruthenium-labeled hepatitis E-specific recombinant antigen.
- 2nd incubation: Biotinylated monoclonal h-IgM-specific antibodies and streptavidin-coated microparticles are added. The 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 II M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined automatically by the software by comparing the electrochemiluminescence signal obtained from the reaction product of the sample with the signal of the cutoff value previously obtained by calibration.

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

Reagents - working solutions

The **cobas e** pack (M, R1, R2) is labeled as AHEVIGM.

M Streptavidin-coated microparticles, 1 bottle, 14.1 mL: Streptavidin-coated microparticles 0.72 mg/mL; preservative.

Elecsys Anti-HEV IgM

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R1 Recombinant HEV antigen~Ru(bpy)$_3^{2+}$, 1 bottle, 19.7 mL:
Hepatitis E antigen labeled with a ruthenium complex > 0.1 µg/mL; HEPES[b] buffer 50 mmol/L, pH 7.2; preservative.

R2 Anti-h-IgM-Ab~biotin, 1 bottle, 19.7 mL:
Biotinylated monoclonal anti-h-IgM antibody (mouse) > 700 ng/mL; HEPES buffer 50 mmol/L, pH 7.2; preservative.

b) HEPES = [4-(2-hydroxyethyl)-piperazine]-ethane sulfonic acid

AHEVIGM Cal1 Negative calibrator 1, 1 bottle of 1.0 mL:
Human serum, negative for anti-HEV IgM; buffer; preservative.

AHEVIGM Cal2 Positive calibrator 2, 1 bottle of 1.0 mL:
Human serum, reactive for anti-HEV IgM; buffer; preservative.

Precautions and warnings

For in vitro diagnostic use for health care professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste:
Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

Warning

H317 May cause an allergic skin reaction.

Prevention:

P261 Avoid breathing mist or vapours.

P272 Contaminated work clothing should not be allowed out of the workplace.

P280 Wear protective gloves.

Response:

P333 + P313 If skin irritation or rash occurs: Get medical advice/attention.

P362 + P364 Take off contaminated clothing and wash it before reuse.

Disposal:

P501 Dispose of contents/container to an approved waste disposal plant.

Product safety labeling follows EU GHS guidance.

Contact phone: all countries: +49-621-7590

All human material should be considered potentially infectious. All products derived from human blood are prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV. The testing methods use assays that have been approved by the FDA or that are in compliance with the legal rules applicable to placing in vitro diagnostic medical devices for human use on the market in the European Union.

The serum containing anti-HEV IgM (AHEVIGM Cal2) was inactivated using β-propiolactone and UV-radiation.

However, as no inactivation or testing method can rule out the potential risk of infection with absolute certainty, the material should be handled with the same level of care as a patient specimen. In the event of exposure, the directives of the responsible health authorities should be followed.[40,41]

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

Reagent handling

The reagents (M, R1, R2) in the kit are ready-for-use and are supplied in **cobas e** packs.

Calibrators:

The calibrators are supplied ready-for-use in bottles compatible with the system.

Unless the entire volume is necessary for calibration on the analyzer, transfer aliquots of the ready-for-use calibrators into empty snap-cap bottles (CalSet Vials). Attach the supplied labels to these additional bottles. Store the aliquots at 2-8 °C for later use.

Perform **only one** calibration procedure per aliquot.

All information required for correct operation is available via the **cobas** link.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the **cobas e** pack **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

Stability of the **cobas e** pack:	
unopened at 2-8 °C	up to the stated expiration date
on the analyzers	16 weeks

Stability of the calibrators:	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	16 weeks
on the analyzers at 20-25 °C	use only once

Store calibrators **upright** in order to prevent the calibrator solution from adhering to the snap-cap.

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, Na-heparin, K_2-EDTA, K_3-EDTA and Na-citrate plasma.

Plasma tubes containing separating gel can be used.

Criterion: Samples with a COI (cutoff index) ≥ 1.0: ± 20 % recovery; samples with a COI < 1.0: ± 0.20 recovery.

Stable for 7 days at 20-25 °C, 14 days at 2-8 °C, 3 months at -20 °C (± 5°C). The samples may be frozen 5 times.

The sample types listed were tested with a selection of sample collection tubes or systems 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/collection system manufacturer.

Specimens should not be subsequently altered with additives (e.g. biocides, anti-oxidants or substances that could possibly change the pH or ionic strength of the sample) in order to avoid erroneous findings.

Centrifuge samples containing precipitates, thawed samples, and samples for repeat measurements before performing the assay.

Do not use heat-inactivated samples.

Do not use samples and controls stabilized with azide.

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

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

The performance of the Elecsys Anti-HEV IgM assay has not been established with cadaveric samples or body fluids other than serum and plasma.

Materials provided

See “Reagents – working solutions” section for reagents.

Elecsys Anti-HEV IgM

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- 2 x 4 bottle labels

Materials required (but not provided)

- REF 09056289190, PreciControl Anti-HEV IgM, 16 x 1.0 mL
- REF 11776576322, CalSet Vials, 2 x 56 empty snap-cap bottles
- REF 07299001190, Diluent Universal, 36 mL sample diluent
- General laboratory equipment
- **cobas e** analyzer

Additional materials for **cobas e** 402 and **cobas e** 801 analyzers:

- REF 06908799190, ProCell II M, 2 x 2 L system solution
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- REF 07485409001, Reservoir Cup, 8 cups to supply ProCell II M and CleanCell M
- REF 06908853190, PreClean II M, 2 x 2 L wash solution
- REF 05694302001, Assay Tip/Assay Cup tray, 6 magazines x 6 magazine stacks x 105 assay tips and 105 assay cups, 3 wasteliners
- REF 07485425001, Liquid Flow Cleaning Cup, 2 adaptor cups to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning Detection Unit
- REF 07485433001, PreWash Liquid Flow Cleaning Cup, 1 adaptor cup to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning PreWash Unit
- REF 11298500316, ISE Cleaning Solution/Elecsys SysClean, 5 x 100 mL system cleaning solution

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.

Place the cooled (stored at 2-8 °C) **cobas e** pack on the reagent manager. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the **cobas e** pack.

Calibrators:

Place the calibrators in the sample zone.

Read in all the information necessary for calibrating the assay.

Calibration

Traceability: No international standard is available for anti-HEV IgM. This method has been standardized against a Roche reference standard. The units have been assigned arbitrarily.

Calibration frequency: Calibration must be performed once per reagent lot using AHEVIGM Cal1, AHEVIGM Cal2 and fresh reagent (i.e. not more than 24 hours since the **cobas e** pack was registered on the analyzer).

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Renewed calibration is recommended as follows:

- after 12 weeks when using the same reagent lot
- after 28 days when using the same **cobas e** pack on the analyzer
- as required: e.g. quality control findings outside the defined limits

Quality control

For quality control, use PreciControl Anti-HEV IgM.

Controls for the various concentration ranges should be run individually at least once every 24 hours when the test is in use, once per **cobas e** pack, 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.

If necessary, repeat the measurement of the samples concerned.

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

Calculation

The analyzer automatically calculates the cutoff based on the measurement of AHEVIGM Cal1 and AHEVIGM Cal2. The result of a sample is given either as reactive or non-reactive as well as in the form of a cutoff index (signal sample/cutoff).

Interpretation of the results

Numeric result	Result message	Interpretation
COI < 1.0	Non-reactive	Negative for anti-HEV IgM
COI ≥ 1.0	Reactive	Positive for anti-HEV IgM

Limitations - interference

The effect of the following endogenous substances and pharmaceutical compounds on assay performance was tested. Interferences were tested up to the listed concentrations and no impact on results was observed.

Endogenous substances

Compound	Concentration tested
Bilirubin	≤ 1129 µmol/L or ≤ 66 mg/dL
Hemoglobin	≤ 0.621 mmol/L or ≤ 1000 mg/dL
Intralipid	≤ 2000 mg/dL
Biotin	≤ 4912 nmol/L or ≤ 1200 ng/mL
Rheumatoid factors	≤ 300 IU/mL
Albumin	≤ 70 g/L
IgG	≤ 70 g/L
IgA	≤ 16 g/L

Criterion: Samples with a COI ≥ 1.0: ± 20 % recovery; samples with a COI < 1.0: ± 0.20 recovery.

As with many µ-capture assays, an interference with unspecific human IgM is observed. Increasing amounts of unspecific human IgM may lead to a decrease in the recovery of positive samples with the Elecsys Anti-HEV IgM assay.

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

In addition, the following special drugs used in hepatitis E therapy were tested. No interference with the assay was found.

Special drugs

Drug	Concentration tested mg/L
Peginterferon alfa-2a	≤ 0.108
Ribavirin	≤ 720
Sofosbuvir	≤ 240

Drug interferences are measured based on recommendations given in CLSI guidelines EP07 and EP37 and other published literature. Effects of concentrations exceeding these recommendations have not been characterized.

In rare cases, interference due to extremely high titers of antibodies to immunological components, 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.

Results may remain negative during HEV infection in immunocompromised patients.

Dilution

Use Diluent Universal for automatic sample predilution.

Specific performance data

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

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Precision

Precision was determined using Elecsys reagents, samples and controls in a protocol (EP05-A3) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day in duplicate each for 21 days (n = 84). The following results were obtained:

cobas e 402 and **cobas e** 801 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean COI	SD COI	CV %	SD COI	CV %
HS[c)] 1	0.131	0.00284	2.2	0.00775	5.9
HS 2	0.616	0.0110	1.8	0.0344	5.6
HS 3	1.37	0.0230	1.7	0.0691	5.1
HS 4	2.79	0.0614	2.2	0.170	6.1
HS 5	6.20	0.112	1.8	0.378	6.1
PC[d)] Anti-HEV IgM 1	0.120	0.00229	1.9	0.00658	5.5
PC Anti-HEV IgM 2	2.94	0.0755	2.6	0.168	5.7

c) HS = human sample (serum/plasma)

d) PC = PreciControl

Analytical specificity

No cross-reactions with samples containing antibodies against HAV, HBV, HCV, HIV, EBV, HSV, Rubella or CMV, samples from autoimmune diseases (AMA and ANA) or non-viral induced liver diseases were observed. Measurements were performed at each of the disease states listed above using ≥ 5 serum or plasma samples.

Seroconversion sensitivity and titer development

Seroconversion sensitivity of the Elecsys Anti-HEV IgM assay was shown by testing 6 commercial seroconversion panels in comparison to 5 other registered anti-HEV IgM assays. The Elecsys Anti-HEV IgM assay detected anti-HEV IgM in 36 out of a total of 88 panel members, while the comparison assays detected 29 (assay A, 1 seroconversion panel not detected), 35 (assay B, 1 seroconversion panel not detected), 30 (+ 3 borderline, assay C, 1 seroconversion panel not detected), 27 (assay D, 1 seroconversion panel not detected), and 41 (assay E) panel members, respectively.

Panel	**Days since first bleeding until anti-HEV IgM reactive**						
	Panel members	**Elecsys Anti-HEV IgM**	**Assay**				
			A	**B**	**C**	**D**	**E**
SCP-HEV-001b	8	41	41	41	49 (46 b[e)])	41	38
SCP-HEV-002b	8	35	35	35	35	42	35
SCP-HEV-003a	12	42	no sc[f)]	42	42	no sc	42
SCP-HEV-005b	20	28	28	28	28	28	28
SCP-HEV-006b	23	50	50	50	50	50	50
SCP-HEV-007a	17	32	32	no sc	no sc (32 b)	32	28

e) initially borderline

f) no seroconversion detectable

Relative sensitivity

Performance of the Elecsys Anti-HEV IgM assay was assessed by testing a total of 657 samples at 3 different study sites in Europe. 440 samples from patients with presumed acute HEV infection and 217 HEV-PCR positive samples were measured with the Elecsys Anti-HEV IgM assay and 3 commercially available anti-HEV IgM assays. Samples from patients with presumed acute hepatitis E infection included 252 samples from Europe (endemic for HEV genotype 3) and 188 samples from Vietnam and Bangladesh (endemic for HEV genotype 1).

Additionally, 50 samples were measured at 1 study site in China (confirmed genotype 4) with the Elecsys Anti-HEV IgM assay and 3 anti-HEV IgM assays commercially available in China.

Samples were considered positive if the result was reactive in all of the comparator assays.

Cohort	**N**	**Elecsys Anti-HEV IgM assay reactive**	**Samples considered anti-HEV IgM positive**	**Sensitivity, % (95 % CI[g)])**
HEV-PCR positive	217	68	69	98.6 (92.2-100)
Presumed acute HEV infection	440	354	359	98.6 (96.8-99.5)
Presumed acute HEV infection (China)	50	49	49	100 (92.7-100)

g) CI = confidence interval, 2-sided

Relative specificity

A total of 8011 samples from blood donors (n = 5040), diagnostic routine (n = 2427), and pregnant women (n = 544) were tested at 4 centers in Europe with the Elecsys Anti-HEV IgM assay and 3 commercially available anti-HEV IgM assays. If samples were non-reactive in 2 out of 3 comparator assays, they were considered negative for anti-HEV IgM.

Cohort	**N**	**Elecsys Anti-HEV IgM assay non-reactive**	**Samples considered anti-HEV IgM negative**	**Specificity, % (95 % CI)**
Blood donors	5040	4977	4995	99.6 (99.4-99.8)
Diagnostic routine[h)]	2427	2348	2375	98.9 (98.4-99.2)
Pregnant women	544	531	531	100 (99.3-100)

h) suspected for viral hepatitis

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39 Seth A, Sherman KE. Hepatitis E: What We Think We Know. Clin Liver Dis 2020;15(Suppl 1):S37-S44.

40 Occupational Safety and Health Standards: Bloodborne pathogens. (29 CFR Part 1910.1030). Fed. Register.

41 Directive 2000/54/EC of the European Parliament and Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work.

For further information, please refer to the appropriate operator's manual for the analyzer concerned, the respective application sheets 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.

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

The Summary of Safety & Performance Report can be found here: https://ec.europa.eu/tools/eudamed

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see dialog.roche.com for definition of symbols used):

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

CE 0123

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