SIEMENS Healthineers

Berichrom® C1-Inhibitor
Berichrom C1-INHIBITOR

CE 0197

Revision bar indicates update to previous version.

Reagents for the determination of C1-inhibitor

Intended Use

Berichrom C1-INHIBITOR is an in vitro diagnostic reagent for the quantitative, WHO-standardized determination of C1-inhibitor activity as an aid to diagnosis of congenital or acquired C1-Inhibitor deficiencies in patients at risk for or suspected to have C1-inhibitor deficiency in human sodium citrated plasma by means of automated, chromogenic methods.

Summary and Explanation

C1-Inhibitor (C1-INH) is a multi-specific protease inhibitor responsible for regulation enzymes of the complement, coagulation, fibrinolytic, and kinin-forming systems. This primary regulator of the contact system inhibits the C1r and C1s subunits of the activated first component of complement, activated coagulation factors FXI and FXII, plasma kallikrein (Fletcher factor) and plasmin. Under conditions of C1-INH deficiency, uncontrolled activation of the contact system leads to overproduction of bradykinin, a potent vasoactive peptide thought to be the primary mediator of angioedema in hereditary angioedema (HAE, or Quincke's edema), an autosomal dominant genetic disorder[1,2]. Acquired C1-INH deficiency goes along with the same symptoms of angioedema.

The bradykinin production induced by C1-INH deficiency results in increased vascular permeability and release of nitric oxide and prostaglandin E, which further increase vasodilation and extravasation of fluid into subcutaneous tissues. These effects manifest as the characteristic edema in HAE of subcutaneous tissues, as well as the submucosa of the gastrointestinal, genitourinary, and upper respiratory tracts. Patients with the more common type (85 % of HAE patients) have low levels of functional C1-INH and C1-INH antigen. Patients with the second form (15 % of HAE patients) have low levels of functional C1-INH but normal or increased levels of C1-INH antigen that is dysfunctional.

Among others one potential approach for prevention and treatment is the administration of C1 inhibitor concentrate[1,3–6].

Principles of the Procedure

Berichrom C1-INHIBITOR in the sample inhibits a receiving volume of C1-esterase. The remaining activity of the C1-esterase is determined by measuring the increase in absorbance at 405 nm in a kinetic test based on the following reactions:

Berichrom C1-INHIBITOR$_{sample}$ + C1-esterase$_{excess}$ ——> [C1-inhibitor-C1-esterase] + C1-esterase$_{remainder}$

MeOC-Lys(ε-Cbo)-Gly-Arg-pNA $\xrightarrow{\text{C1-esterase}_{remainder}}$ MeOC-Lys(ε-Cbo)-Gly-Arg-OH + p-nitroaniline

Reagents

Note: Berichrom C1-INHIBITOR can be used manually or on automated coagulation analyzers. Siemens Healthineers provides Reference Guides (Application Sheets) for several coagulation analyzers. The Reference Guides (Application Sheets) contain analyzer/assay specific handling and performance information which may differ from that provided in these Instructions for Use. In this case, the information contained in the Reference Guides (Application Sheets) supersedes the information in these Instructions for Use. Please also consult the instruction manual of the instrument manufacturer!

Reagent	Description	Storage	Stability
Berichrom® C1-Inhibitor Berichrom C1-INHIBITOR			
REAGENT E	Lyophilized reagent containing: • C1-Esterase, human • Stabilizers • Preservatives: • reaction mass of 5-chloro-2-methyl-2H-isothiazol-3-one / 2-methyl-2H-isothiazol-3-one (3:1) (reconstituted: 10 mg/L)	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	37 °C: reconstituted, 8 hours; 30 °C: reconstituted, 1 day; 15–25 °C: reconstituted, 1 week; 2–8 °C: reconstituted, 2 weeks; ≤ –20 °C: reconstituted, 1 month
SUBSTRATE	Lyophilized reagent containing: • C1-Esterase Substrat (reconstituted: 5 mmol/L)	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	37 °C: reconstituted, 1 week; 30 °C: reconstituted, 2 weeks; 15–25 °C: reconstituted, 2 weeks; 2–8 °C: reconstituted, 6 weeks; ≤ –20 °C: reconstituted, 6 months
SUBSTRATE DILUENT	Ready to use liquid containing: • Poloxamer	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	n/a

Stored in their original vials Berichrom C1-INHIBITOR REAGENT E can be frozen up to 3 times, Berichrom C1-INHIBITOR SUBSTRATE up to 10 times.

On-board stability
Information regarding on-board stability is specified in the Reference Guides (Application Sheets) for the different coagulation analyzers.

Warnings and Precautions

For *in-vitro* diagnostic use only.

For laboratory professional use.

According to EU regulation 2017/746, any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the EU Member State in which the user and/or patient is established.

Safety data sheets (MSDS/SDS) available on siemens-healthineers.com/sds.

Warning! Berichrom C1-INHIBITOR REAGENT E
Hazardous ingredient: reaction mass of 5-chloro-2-methyl-2H-isothiazol-3-one / 2-methyl-2H-isothiazol-3-one (3:1) (0.0603 % [w/w]), Trypsin inhibitor (0.466 % [w/w]).
H315: Causes skin irritation. **H319**: Causes serious eye irritation. **H317**: May cause an allergic skin reaction. **H411**: Toxic to aquatic life with long lasting effects.
P261: Avoid breathing dust. **P264**: Wash hands thoroughly after handling. **P273**: Avoid release to the environment. **P280**: Wear protective gloves/protective clothing/eye protection/face protection. **P302 + P352**: IF ON SKIN: Wash with plenty of soap and water. **P333 + P313**: If skin irritation or rash occurs: Get medical advice/attention. **P362 + P364**: Take off contaminated clothing and wash it before reuse. **P337 + P313**: If eye irritation persists: Get medical advice/attention. **P391**: Collect spillage. **P501**: Dispose of contents and container in accordance with all local, regional, and national regulations.

Warning! Berichrom C1-INHIBITOR SUBSTRATE
Hazardous ingredient: C1-Esterase Substrat (29.1 % [w/w]).
H302: Harmful if swallowed.
P264: Wash hands thoroughly after handling.

CAUTION! POTENTIAL BIOHAZARD
Berichrom C1-INHIBITOR REAGENT E
Each donor or donor unit was tested and found to be negative for human immunodeficiency virus (HIV) 1 and 2, hepatitis B virus (HBV) and hepatitis C virus (HCV) using either tests that are CE marked or FDA approved for this purpose. Because no known test can offer complete assurance of the absence of infectious agents, all human derived products should be handled with appropriate caution.

Caution
Berichrom C1-INHIBITOR REAGENT E
This device contains material of animal origin and should be handled as a potential carrier and transmitter of disease.

Contains sodium azide as a preservative. Sodium azide can react with copper or lead plumbing to form explosive metal azides. On disposal, flush reagents with a large volume of water to prevent the buildup of azides. Disposal into drain systems must be in compliance with prevailing regulatory requirements.

Dispose of hazardous or biologically contaminated materials according to the practices of your institution. Discard all materials in a safe and acceptable manner and in compliance with all government requirements.

Preparing Reagents

Berichrom C1-INHIBITOR REAGENT E: Dissolve vial contents in the labeled amount of distilled water.

Berichrom C1-INHIBITOR SUBSTRATE: Dissolve vial contents in the labeled amount of Berichrom C1-INHIBITOR SUBSTRATE DILUENT.

Mix reagents carefully once more before using.

Specimen Collection and Handling

Collecting the Specimen

To obtain the plasma, carefully mix 1 part sodium citrate solution 0.11 mol/L (3.2 %) with 9 parts venous blood, avoiding the formation of foam. Centrifuge the blood specimen immediately at

1 500 × g for no less than 15 minutes at room temperature. Please refer to CLSI guideline H21-A5[7] for further details.

Storing the Specimen

In some cases the assay may be performed using serum, however the plasma and serum values do not always correlate.

Stability of the samples:

≤ –20 °C	2 weeks
2 to 8 °C	2 days
15 to 25 °C	4 hours

Plasma stored at ≤ –20 °C is to be thawed within 10 minutes at 37 °C after which the assay is to be performed within 2 hours.

Procedure

Materials Provided

REF	Contents		
OUIA15	Berichrom® C1-Inhibitor Berichrom C1-INHIBITOR		
	C1-Esterase Berichrom C1-INHIBITOR REAGENT E	3 × →	5 mL
	Substrate Reagent Berichrom C1-INHIBITOR SUBSTRATE	3 × →	1 mL
	Substrate Solvent Berichrom C1-INHIBITOR SUBSTRATE DILUENT	1 ×	3 mL

Materials Required but not Provided

Item	Description
REF ORKL17	STANDARD PLASMA, Standard Human Plasma
REF ORKE41	CONTROL N, Control Plasma N
REF OUPZ17	CONTROL P, Control Plasma P
–	Acetic acid 20 % (only for the two-point method)
REF B4234-25 REF B4265-37 –	OV BUFFER, Dade® Owren's Veronal Buffer or CA SYSTEM BUFFER, Dade® CA System Buffer or Isotonic Saline Solution
Coagulation analyzers[a], such as:	• Atellica® COAG 360 System • BCS® XP System • SYSMEX CS-2000i/CS-2100i System • SYSMEX CS-2500 System • SYSMEX CS-5100 System

[a] Availability of analyzers may vary by country.

Please note that the applications on other analyzers can be validated by the instrument manufacturer in accordance with the requirements of the REGULATION (EU) 2017/746 under their responsibility as long as the intended purpose and performance are not modified.

Test Procedure

Semi-micro test:

Cuvette:	1 cm path length
Wavelength:	405 nm
Test temperature:	optionally 25 °C, 30 °C or 37 °C

Pipetting scheme for the kinetic method

Pre-warm Berichrom C1-INHIBITOR REAGENT E, Berichrom C1-INHIBITOR SUBSTRATE and plastic cuvettes/ tubes to the selected test temperature.

	C1-esterase enzyme value (CEV)	Sample
Isotonic saline	20 µL	–
Plasma sample	–	20 µL
Berichrom C1-INHIBITOR REAGENT E	1 000 µL	1 000 µL
Mix and incubate at selected test temperature for exactly 5 minutes		
Berichrom C1-INHIBITOR SUBSTRATE	100 µL	100 µL
Mix and determine $\Delta A_{405\ nm}$/minutes Photometer/Stopwatch: Read the absorbance within 30 seconds and start the stopwatch simultaneously. Read the absorbance again after exactly 60–120 seconds, and calculate the respective ΔA/minute values by subtraction, and calculate the mean of the two values.		

Evaluation, kinetic method

Each assay series requires at least one C1-esterase enzyme value ($\Delta A/minute_{cev}$) and one reference measurement value, which is determined by using a reference plasma with an assigned value for C1-INH (e. g. STANDARD PLASMA) as the sample. These values are used to calculate the laboratory-internal factor F_L:

$$F_L = \frac{\text{Assigned value (\% of Norm)}_{\text{reference plasma}}}{\Delta A/\text{minute}_{\text{cev}} - \Delta A/\text{minute}_{\text{reference plasma}}}$$

The C1-inhibitor content of the sample in % of Norm can then be calculated from the following formula:

$$\text{C1-inhibitor}_{\text{sample}}\ (\%\ \text{of Norm}) = F_L \times (\Delta A/\text{minute}_{\text{cev}} - \Delta A/\text{minute}_{\text{sample}})$$

Pipetting scheme for the two-point method

Pre-warm Berichrom C1-INHIBITOR REAGENT E, Berichrom C1-INHIBITOR SUBSTRATE and plastic cuvettes/ tubes to 37 °C.

	C1-esterase enzyme value (CEV)	Sample	Sample blank
Isotonic saline	20 µL	–	1 100 µL
Plasma sample	–	20 µL	20 µL
Berichrom C1-INHIBITOR REAGENT E	1 000 µL	1 000 µL	–
Mix and incubate for exactly 5 minutes at 37 °C.			
Berichrom C1-INHIBITOR SUBSTRATE	100 µL	100 µL	–
Mix immediately and start the stopwatch simultaneously. After exactly 2 minutes, add:			
Acetic acid 20 %	500 µL	500 µL	500 µL
Mix immediately and read the absorbance against the sample blank within 60 minutes.			

Evaluation, two-point method

Each assay series requires at least one C1-esterase enzyme value (A_{CEV}) and one reference measurement value, which is determined by using a reference plasma with an assigned value for C1-inhibitor (e. g. STANDARD PLASMA) as the sample. These values are used to calculate the laboratory-internal factor F_L:

$$F_L = \frac{\text{Assigned value (\% of Norm)}_{\text{reference plasma}}}{A_{CEV} - A_{\text{reference plasma}}}$$

The C1-inhibitor content of the sample in % of Norm can then be calculated from the following formula:

$C1\text{-inhibitor}_{sample}$ (% of Norm) = F_L x (A_{CEV} – A_{sample})

Notes

1. Doubling or halving the volumes used in the test mixtures has no effect on the calculation or laboratory-internal calculation factor.
2. F_L is a calculation factor established within the laboratory and needs to be determined only once in an assay series. This method of evaluation is not dependent on the selected test temperature and is basically equivalent to an evaluation via a reference curve.
3. If the sample has a C1-inhibitor content above 150 % of Norm, the assay should be repeated using a sample prediluted 1+1 with isotonic saline. In this case the result is then multiplied by 2. If the sample has a C1-inhibitor content below 20 % of Norm it is recommended to use 40 µL sample in the test. The result is divided by 2.
4. The laboratory-internal factor F_L or the calibration curve must be re-determined for each change of device and for each new lot of Berichrom C1-INHIBITOR.

Internal Quality Control

Normal range: CONTROL N

Pathological range: CONTROL P

Two controls should be measured with each calibration and at least every 8 hours during each testing day (one in the normal range and one in the pathological range). The controls should be processed just like the samples. Each laboratory should determine its own quality control range, either by means of the target values and ranges provided by the manufacturer of the controls or by means of its own control range established in the laboratory. If the measured control value lies outside the previously established range, then the reagents, the laboratory-internal factor F_L and/or the calibration curve and the coagulation analyzer should be examined. Do not release patient results until the cause of deviation has been identified and corrected.

Limitations

Turbidity and particles in the samples may interfere with the assay. Therefore, samples containing particles must be centrifuged prior to testing. Lipemic or turbid samples which cannot be clarified by centrifugation (10 minutes at approximately 15 000 × g) must be excluded from the assay.

Siemens Healthineers has validated use of these reagents on various analyzers to optimize product performance and meet product specifications. Please note that the applications on other analyzers can be validated by the instrument manufacturer in accordance with the requirements of the REGULATION (EU) 2017/746 under their responsibility as long as the intended purpose and performance are not modified. User defined modifications are not supported by Siemens Healthineers as they may affect performance of the system and assay results. It is the responsibility of the user to validate modifications to these instructions or use of the reagents on analyzers other than those included in Siemens Healthineers Application Sheets or these Instructions for Use.

Results of this test should always be interpreted in conjunction with the patient's medical history, clinical presentation and other findings.

Expected Values

70 to 130 % of Norm[7]

Reference intervals vary from laboratory to laboratory depending on the population served and the technique, method, equipment and reagent lot used. Therefore, each laboratory must establish its own reference intervals or verify them whenever one or more of the aforementioned variables are changed.

Performance Characteristics

Measuring Range

The measuring range depends on the individual application of the assay due to instrument related conditions. Application specific performance data is listed in the respective Reference Guides of the instruments.

Precision

The precision of Berichrom C1-INHIBITOR on the BCT was estimated with CONTROL N and CONTROL P from a total of 8 separate runs over 5 testing days. The intra-assay coefficients of variation (CV) ranged between 1.8 and 7.9 % and the inter-assay CV were between 3.2 and 6.6 %.

The reproducibility was assessed by Siemens Healthineers for Berichrom C1-INHIBITOR based on publicly available proficiency testing information in 2020. The overall reproducibility median CV% was found to be < 10 % including lot, instrument, laboratory and operator variability factors.

Technical Assistance

For customer support, contact your local technical support provider or distributor.

siemens-healthineers.com

Current Version of Application Sheets

Berichrom C1-INHIBITOR can be used in combination with various automated coagulation analyzers. Siemens Healthineers provides Reference Guides/Application Sheets for the coagulation analyzers listed in section "Materials Required but not Provided", page 4 under the dedicated link below:

siemens-healthineers.com/rg

As Siemens Healthineers continuously monitors the product performance and safety, the users are required to ensure that they work with the correct revision of the instructions for the product lots in use. Please periodically review the availability of new electronic labeling revisions to ensure safe use of the product.

The IFU version number is visible on each product box label. Siemens Healthineers ensures that all products lots bearing the same IFU version number are compatible with the electronic labeling provided via siemens-healthineers.com/eIFU.

References

1. Levi M, Cohn DM, Zeerleder S. Hereditary angioedema: Linking complement regulation to the coagulation system. Res Pract Thromb Haemost. 2018;3(1):38-43.
2. Csuka D, Veszeli N, Varga L, et al. The role of the complement system in hereditary angioedema. Mol Immunol 2017;89:59-68.
3. Henry Li H, Riedl M, Kashkin J. Update on the Use of C1-Esterase Inhibitor Replacement Therapy in the Acute and Prophylactic Treatment of Hereditary Angioedema. Clin Rev Allergy Immunol 2019;56(2):207-218.
4. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. J Allergy Clin Immunol Pract. 2021;9(1):132-50.
5. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema - The 2017 revision and update. Allergy. 2018;73(8):1575-96.
6. Longhurst H, Cicardi M, Craig T, et al. COMPACT Investigators. Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor. N Engl J Med. 2017;376:1131-1140.
7. CLSI. Collection, Transport, and Processing of Blood Specimens for Testing Plasma-Based Coagulation Assays and Molecular Hemostasis Assays. Approved Guideline – Fifth Edition. CLSI document **H21-A5** [ISBN 1-56238-657-3]. CLSI, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898 USA, 2008.

Definition of Symbols

The following symbols may appear on the product labeling:

	Do not reuse		Use By
LOT	Batch Code	REF	Catalogue Number
	Caution		Manufacturer
EC REP	Authorized representative in the European Community		Contains sufficient for <n> tests
	Biological Risks	IVD	*In Vitro* Diagnostic Medical Device
	Temperature Limitation		Consult instruction for Use
	Non-sterile		CE marking of conformity
CE 0197	CE marking of conformity with notified body ID number. Notified body ID number can vary.	CONTENTS	Contents
	Reconstitution volume	LEVEL	Level
	Keep away from sunlight and heat	WARNING	Warning
DANGER	Danger	RxOnly	Prescription device (US only)
UDI	Device Identification (UDI) barcode	REACH xx/xx/xx	REACH Authorization Number

Legal Information

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