PrecisionBioLogic

CRYO*check*™ IVD

LUPUS NEGATIVE CONTROL

Intended Use

CRYO*check* Lupus Negative Control is prepared from human plasma and is recommended as a negative control in assays for lupus anticoagulant. For in vitro diagnostic use.

Summary and Principle

Lupus anticoagulants (LA) are heterogeneous autoantibodies, mainly of the IgG and IgM type, which are directed against phospholipids (PL) or phospholipid-protein complexes involved in coagulation[1]. LA antibodies are detected in patients' plasma by PL-dependent clotting assays. There is a significant association between LA and increased risk of clinical complications such as thrombotic events[2,3] and recurrent fetal loss[4]. Medical diagnosis of LA is based on clinical symptoms and laboratory results. There is no gold standard test for LA. Considering the complexity of mechanism and the heterogeneous nature of LA antibodies, application of different clotting tests that work based on different principles has been recommended[5].

LA prolongs clot formation of PL-dependent coagulation (LA screening) tests in vitro, such as LA-sensitive activated partial thromboplastin time (APTT) or dilute Russell's Viper Venom Time (dRVVT) screen. To confirm the presence of LA in a plasma sample, correction of a prolonged clot time by extra PL (an LA confirmatory test) needs to be performed by laboratories as well as ruling out other abnormalities, such as factor deficiency and heparin presence[5].

CRYO*check* Lupus Negative Control is for use as a negative control in assays for lupus anticoagulant.

Reagents

CRYO*check* Lupus Negative Control contains citrated human plasma collected from donors that have tested negative in accordance with the revised criteria of the SSC Subcommittee for the Standardization of Lupus Anticoagulants[5]. Source plasmas are processed in a manner that yields platelet-poor plasmas. Plasma is then buffered, aliquoted and frozen at very low temperatures. For prescription use only.

Storage, Preparation and Handling

When stored at -40 to -80 °C, CRYO*check* Lupus Negative Control is stable to the end of the month indicated on the product packaging.

Thaw each vial at 37 °C (± 1 °C) in a waterbath**. The use of a dry bath or heating block for thawing is not recommended.** Thawing times are important and should be strictly adhered to. The use of a timer is recommended. Refer to the Thawing Table for recommended thawing times based on aliquot size. Allow thawed plasma to acclimate to room temperature (18 to 25 °C) and invert gently prior to use.

Thawing Table	
Aliquot Size	**37 °C (± 1 °C) Waterbath**
0.5 mL	3 minutes
1.0 mL	4 minutes

Once thawed, CRYO*check* Lupus Negative Control may be used for up to 8 hours on board the analyzer, or for 8 hours if capped in the original vial and maintained at 2 to 8 °C. Allow refrigerated plasma to acclimate to room temperature (18 to 25 °C) and invert gently prior to use. **Thawed materialshould be discarded after eight hours and should not be refrozen.**

Availability

Product	Catalog #	Format
CRYO*check* Lupus Negative Control	CCLN-05	25 vials x 0.5 mL
	CCLN-10	25 vials x 1.0 mL

Instruments

Each lab should prepare the local instrument in accordance with themanufacturer's instructions for use.

Procedure

After thawing and preparing CRYO*check* Lupus Negative Control, use in accordance with established laboratory procedures for the quality control of assays for LA.

Materials Provided

- CRYO*check* Lupus Negative Control

Materials Required but not Provided

- Waterbath capable of maintaining 37 °C (± 1 °C)
- Floatie for thawing vials in waterbath
- Assay reagents
- Coagulation instrument or assay system
- Timer

Results

Control results should fall within the laboratory's established QC ranges provided the integrity of the test system has not been compromised.

Quality Control

Each laboratory should establish its own quality control (QC) ranges using acceptable statistical methods. These QC ranges may then be used to monitorand validate the integrity of the test system[6].

For all coagulation tests, the laboratory must include at least two levels of control for every eight hours of operation and any time a change in reagents occurs[7].

Limitations of the Procedure

When proper control values are not obtained, assessment of each component of the test system including reagents, control plasmas, instrumentation and operator technique must be undertaken in order to ascertain that all other components are functioning properly.

Expected Values

Quality control testing yielded the following results with a representative lot of CRYO*check* Lupus Negative Control. Results may vary depending on instrument, method and technique used. Refer to the Assay Certificate for results specific to each lot of control.

Lupus Anticoagulant Assays	Result	Interpretation
Dilute Russell's Viper Venom Time (dRVVT)	0.87 ratio	Negative
Hexagonal Lupus Anticoagulant	2.0 sec	Negative
Platelet Neutralization Procedure (PNP)	-1.6 sec	Negative

Performance Characteristics

Precision

A precision study was performed by testing CRYO*check* Lupus Negative Control (CCLN) with a qualitative hexagonal phase phospholipid neutralization test for lupus anticoagulant (CRYO*check* Hex LA) on each of 20 days on a Stago STA-R Evolution analyzer. On each day, CCLN was tested in duplicate with three different lot numbers of CRYO*check* Hex LA in two runs, separated by a minimum of two hours, for a total of 240 measurements. The result for CCLN was LA negative for all measurements. The results demonstrated a pooled within lab precision (S_{lab}) of 2.6.

Pooled Data			
N	**Mean (s)**	**Between-Lot (S_{BL})**	**Within-Lab (S_{Lab})**
240	0.2	1.9	2.6

Reproducibility

A reproducibility study was conducted by testing CRYO*check* Lupus Negative Control (CCLN) with CRYO*check* Hex LA at three sites (one internal and two external) by different operators on Stago STA-R Evolution analyzers. At each site, CCLN was tested in triplicate with three different lot numbers of CRYO*check* Hex LA on each of five days, in two runs, separated by a minimum of two hours, for a total of 270 measurements. The result for CCLN was LA negative for all measurements. The results demonstrated a pooled reproducibility of 3 SD.

Pooled 3-site Data											
N	Mean (s)	Repeatability		Between-Run		Between-Day		Between-Site		Reproducibility	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
270	-0.9	1.9	N/A	0.9	N/A	0.0	0.0	0.0	0.0	3.0	N/A

Precautions / Warnings

Do not use the product if it is thawed upon receipt or if the vials appear cracked. Transferring the material into another container other than siliconized glass or polypropylene could have a performance impact and is not recommended.

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

All blood products should be treated as potentially infectious. Source material from which this product was derived was found to be negative when tested in accordance with current required tests for transfusion-transmitted diseases. No known test methods can offer assurance that products derived from human blood will not transmit infectious agents. Accordingly, these human blood-based products should be handled and discarded as recommended for any potentially infectious human specimen[8].

Bibliography

1. Bertolaccini ML, Roch B, Amengual O, Atsumi T, Khamashta MA, Hughes GRV. Multiple antiphospholipid tests do not increase the diagnostic yield in antiphospholipid syndrome. Br. J. Rheumatol. 1998;37(11):1229-1232.
2. Male C, Foulon D, Hoogendoorn H, Vegh P, Silverman E, David M, Mitchell L. Predictive value of persistent versus transient antiphospholipid antibody subtypes for the risk of thrombotic events in pediatric patients with systemic lupus erythematosus. Blood. 2005;106(13):4152-4158.
3. Galli M, Luciani D, Bertolini G, Barbui T. Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. Blood. 2003;101(5):1827-1832.
4. Lockshin MD, Kim M, Laskin CA, Guerra M, Branch DW, Merrill J, Petri M, Porter TF, Sammaritano L, Stephenson MD, Buyon J, Salmon JE. Prediction of adverse pregnancy outcome by the presence of lupus anticoagulant, but not anticardiolipin antibody, in patients with antiphospholipid antibodies. Arthritis Rheum. 2012;64(7):2311-2318.
5. Pengo V, Tripodi A, Reber G, Rand JH, Ortel TL, Galli M, deGroot PG. Update of the guidelines for lupus anticoagulant detection. J. Thromb. Haemost. 2009;7(10):1737-1740.
6. Cembrowski GS, Carey RN. Laboratory quality management. Chicago: ASCP Press; 1989. p. 166-171.
7. CLIA 2004 – Code of Federal Regulations, 42CFR493.1269, 2004
8. U.S. Department of Health and Human Services; Public Health Service. Biosafety in Microbiological and Biomedical Laboratories-Sixth Edition. Centers for Disease Control and Prevention, National Institutes of Health. Atlanta, GA (USA); 2020.CLSI. Laboratory Testing for the Lupus Anticoagulant; Approved Guideline. CLSI H60-A. Wayne, PA (USA); 2014.
9. CLSI. Laboratory Testing for the Lupus Anticoagulant; Approved Guideline. CLSI H60-A. Wayne, PA (USA); 2014.

Symbols Used

IVD	In vitro diagnostic medical device		Biological risks
LOT	Batch code		Manufacturer
REF	Catalogue number	EC REP	Authorized representative in the European Community / European Union
	Use by date	**Rx ONLY**	For prescription use only
	Temperature limit		Consult electronic instructions for use

EC REP European Authorized Representative (Regulatory affairs only)
Emergo Europe— Westervoortsedijk 60, 6827 AT Arnhem, The Netherlands

UKRP United Kingdom Responsible Person
Emergo Consulting (UK) Limited —c/o Cr 360—UL International
Compass House, Vision Park Histon, Cambridge, CB24 9BZ United Kingdom

Precision BioLogic Inc.
140 Eileen Stubbs Avenue | Dartmouth, Nova Scotia | B3B 0A9 | Canada

Tel: 1.800.267.2796 / +1.902.468.6422
Fax: 1.800.267.0796 / +1.902.468.6421

www.precisionbiologic.com