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Package insert, version 9, deks@deks.dk

INR Kalibrator Normal

Product code 2004 DK LOT **13-05** **2022** IVD CE

Assigned Values

P-Coagulation, tissue factor-induced; rel.time	**1,00 INR**	U = 0,025 INR
P-Coagulation, tissue factor-induced; arb.subst.c.	**1 arb.unit/L**	
P-Fibrinogen (340 000); sust.c.	8,93 µmol/L	U = 0,16 µmol/L

Please note: *The values mentioned above are not adjusted for dilution at sampling and should only be used if you do not use citrate-dilution, or if you do not want to include the correction in the calibrating function. If you use citrate tubes when sampling with the dilution proportion of 9 parts full blood to 1 part natrium citrate and want this included in the calibration, the following fibrinogen concentration must be used:*

10,71 µmol/L

P-Antithrombin; arb.subst.c.	**1,05· 10^3 IU/L**	U = 0,027· 10^3 IU/L
P-Protein S; arb.subst.c.	**1,05· 10^3 IU/L**	U = 0,034· 10^3 IU/L
P-Protein C; arb.subst.c.	**1,10· 10^3 IU/L**	U = 0,028· 10^3 IU/L

Expected Use

The material can be used for calibrating of the following quantities:

- P-Coagulation, tissue factor-induced; rel.time (actual/norm; INR; 67/40)

  Calibration hereof also takes the use of DEKS's INR Calibrator Therapeutic and INR Calibrator High
- P-Coagulation, tissue factor-induced; arb.sust.c. (coag.; proc.)
- P-Fibrinogen
- P-Antithrombin
- P-Protein C
- P-Protein S

The calibrator can furthermore be used for the determination of:

- Normal coagulation time for the test P-Coagulation, surface-induced; time.

Receipt

Receiving the samples, check that the samples are frozen.
Are the samples *not* frozen, the validity can be reduced, or the samples can be totally useless – please contact DEKS.

Safety

Each plasma sample included in the material is tested and found negative for HIV 1/2 antibodies, HbsAg and HCV-antibodies.
The samples and their waste products must be handled as patient samples, that are potentially contagious, in accordance with the laboratory's internal instructions and good laboratory practice. The samples may only be

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handled by educated persons qualified to perform calibration.
The samples may not be used for calibration if they were thawed at receipt, have exceeded the shelf-life or maximum in-use stability after thawing or if they have been thawed-frozen-and-thawed again as the assigned values may be altered.

Material

The calibrator is produced from plasma from 30 healthy persons. Full blood is at collection diluted with natrium citrate 0,105 M in the proportion 9 parts blood plus 1part citrate. The plasma is separated by double centrifugation and frozen at -80 ºC. The separate portions are thawed and mixed in a pool, which is then aliquoted in vials of 0,5 ml (filling volume). The material is frozen and kept at -80°C.

Shelf-life

The calibrator is at -80 °C valid until August 2022 and at –20°C it is valid for two weeks.

In-use Stability

After thawing the calibrator can be used for a maximum of 4 hours.

Calibration of Analytical Equipment

Analytical equipment should as minimum be calibrated following the change of reagent batch, following equipment adjustments or when service has been made on the equipment. Calibration must always be performed when the internal controls show a need.
Calibration must be performed with equipment and with a reagent intended for the relevant tests and in correspondence with the manufacturer of the equipment's procedure. The equipment must be maintained and adequately suited for the examination of the chosen components.

Handling and Use

Thawing and preparation of the calibrator

1. The calibrator is thawed in a water bath at 37 °C in exactly 5 minutes, mixed in a turning device at ambient temperature for 5-10 minutes.
   Mixing without a turning device is possible by holding the calibrator between thumb and index finger and tilting it carefully 180º approx. 20 times.
   The calibrator must have room temperature before use.

Further steps at the calibrating of INR

1. Coagulation times for INR Calibrator Therapeutic, Coagulation calibrator *Normal* and INR Calibrator High is decided with the laboratory's routine method.
   At least five measurements are made on each set of material. Mean values of the results are calculated. If one result deviates more than 5% from the mean value, the result should be omitted.

2. Find the spreadsheet:

   www.deks.dk/laboratorier/pakningsvedlaeg

   and fill in the measurement results in the spreadsheet[1]. USE ONLY THE LATEST VERSION OF THE SPREADSHEET AND CHECK THAT THE VALUES ARE CONSISTENT WITH THE USED LOT OF CALIBRATORS. The spreadsheet calculates 'Mean Normal Prothrombin Time' (MNPT) and 'International Sensitivity Index' (ISI) and follows the principle from van den Besselaar, et al. [4].

Value Assignment and Traceability

Coagulation, tissue factor-induced; rel.time, (actual/norm; INR; IRP 67/40) is determined with the manual reference method with use of the international reference preparations WHO 4th International Standard Thrombo-

[1] The spreadsheet performs a orthogonal regression as described by van den Besselaar, AMHP [4].

plastin, Human, Recombinant, Plain (rTF/09) and WHO International Standard Thromboplastin, Rabbit, Plain (RBT/05) [1,2].

The assignment was performed by 3 Nordic expert laboratories, Linköping University Hospital, Haukeland University Hospital in Bergen and Roskilde Hospital in Roskilde. The measurements are performed by each expert laboratory as 3 independent determinations in relation to a protocol, that complies with the WHO guidelines [3]. The expanded uncertainty, U, that indicates the 95%-confidence interval of the value (1,00 INR), is determined to 0,025 INR with the expansion factor k=2,0.

P-Coagulation, tissue factor-induced; arb.subst.c. The value is per definition 1 arb.unit./L solely defined from the production procedure which is a pool of plasma from at least 30 healthy, non-medicated persons. As there are large inter-individual differences of the coagulation factors, there can be lot to lot differences, even with the stated amount of plasmas in the pool. By measuring with a routine reagent (Roskilde Sygehus, 2014), the following activity proportions between the produced lots of normal calibrators is found:
1st national normal plasma 1992: 105%, 2nd national normal plasma 1999: 100%, 3rd national normal plasma 2004: 110% and 4th national normal plasma 2014: 100%.
This implies that when you change from LOT 04-09 to LOT 13-05 you can expect a change of level of up to 10%.

P-Antitrombin; arb subst.c. is assigned using the to 3rd International Standard for Antithrombin, Plasma (08/258) and with use of a chromogen method. The measurements were performed at Clinical Biochemistry Department, Roskilde Hospital. The assigned value is *not* adjusted for any potential dilution with anti-coagulants. The expanded uncertainty, U, that indicates the 95%-confidence interval of the assigned value has an expansion factor k=2,0.

P-Fibrinogen; subst.c. The value is assigned using the 3rd Internationale Reference Preparation (WHO 09/264) using methods based on von Clauss´s method [De Maat MPM et al. 1999]. The measurements were performed at Clinical Biochemistry Department, Roskilde Hospital and at clinical Biochemistry, Slagelse Hospital. The assigned value 8,93 µmol/L does not take into consideration that patient samples are usually diluted with anti-coagulants. Therefore, an adjusted value of 10,71 µmol/L is used, if compensation is necessary for the average dilution of patient samples when 9 parts full blood is stabilized with 1 part citrate solution, and plasma is therefore diluted approx. 20%. The expanded uncertainty, U, that indicates the 95%-confidence interval is determined to 0,16 µmol/L with an expansion factor k=2,0.
The value of the last lot of DEKS's Normal calibrator is originally assigned with the 2nd WHO fibrinogen reference preparation, and at re-tested with the 3rd WHO reference preparation (09/264), has a 7% higher value. This level change is confirmed with data from the external quality assurance program. This means that when you change from lot 04-09 to lot 13-05 you can expect a level change of approx. 7%.

P-Protein C; arb subst.c. is assigned using the 2nd International Standard for Protein C (02/342). The measurements were performed at Clinical Biochemistry Department, Roskilde Hospital. The value is not adjusted for any potential dilution with anti-coagulants. The expanded uncertainty, U, that indicates the 95%-confidence interval of the assigned value has an expansion factor k=2,0.

P-Protein S; arb subst.c. is assigned using the 2nd International Standard for Protein S (03/228). The measurements were performed at Clinical Biochemistry Department, Roskilde Hospital. The value is not adjusted for any potential dilution with anti-coagulants. The expanded uncertainty, U, that indicates the 95%-confidence interval of the assigned value has an expansion factor k=2,0.

Reference

In addition to Coagulation Calibrator *Normal* DEKS also offers INR Calibrator *Therapeutic* (product code 3346 DK) og INR Calibrator *High* (product code 3252 DK) for calibrating the quantity P-Coagulation, tissue factor-induced; rel.time (actual/norm; INR; IRP 67/40).

Ordering and Shipment of the Calibrator

Coagulation Calibrator *Normal* is found in packages of 2 vials and can be ordered via DEKS.
The order is placed via the on-line ordering system at www.deks.dk.
DEKS can be reached at tel. +45 3863 4400 or e-mail: deks@deks.dk.
The materials are shipped as dry-ice shipment.

Expert

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Literature references

[1] The National Institute for Biological Standards and Control (NIBSC), WHO 4th International Standard Thromboplastin, Human, Recombinant, Plain, NIBSC code: rTF/09, Instructions for use (Version 2.0). 1-3. 2012-11-30.

[2] The National Institute for Biological Standards and Control (NIBSC), WHO International Standard Thromboplastin, Rabbit, Plain, NIBSC code: RBT/05, Instructions for use (Version 3.0). 1-3. 2012-12-13.

[3] WHO, WHO Expert Committee Biological Standardization, Guidelines for thromboplastins and plasma used to control oral anticoagulant therapy with vitamin K antagonists. 271-364. 2013. Genova. WHO Technical Report Series no. 979.

[4] van den Besselaar, AMHP. *et al*. Journal of Thrombosis and Haemostasis. 1946-1953, 2, 2004.

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Revision history

2014-01-30: Version 1.

2014-09-02: Version 2. Added reference values for antithrombin, fibrinogen, protein C and protein S. Restructured the order of sections. Editorial changes

2015-05-07: Version 3. A small adjustment of the value of fibrinogen from ~~8,88 µmol/L~~ to 8.93 µmol/L due to more reference tests

2016-07-05: Version 4. Corrected a spelling mistake in the reference material used for Protein C. Updated contact information

2017-01-02: Version 5. New DEKS logo

2017-12: Version 6. New document template

2019-01: Version 7. A few linguistic corrections

2019-08: Version 8. A few linguistic corrections

2020-01: Version 9. A new link www.deks.dk/laboratorier/pakningsvedlaeg and linguistic corrections