Medicines & Healthcare products Regulatory Agency

NIBSC Confidence in Biological Medicines

WHO International Standard
2nd International Standard 2016 Coagulation Factor XI, Plasma, Human
1st International Standard 2017 Coagulation Factor XII, Plasma, Human
NIBSC code: 15/180
Instructions for use
(Version 2.0, Dated 20/12/2017)

1. INTENDED USE

This material is the 2nd International Standard for Factor XI, Plasma, Human and the 1st International Standard for Factor XII, Plasma, Human. It consists of ampoules, coded 15/180, containing approximately 1 mL aliquots of human normal plasma, freeze-dried. This preparation is intended for use in the measurement of FXI functional activity (FXI:C) and antigen (FXI:Ag) and FXII functional activity (FXII:C) and antigen (FXII:Ag) in plasma. In addition it can be used for potency assignment of FXI therapeutic concentrates.

The ECBS reports are available from the WHO (www.who.int/entity/biologicals/ECBS_2016_BS2281_FXI-2nd_IS_final.pdf)
http://www.who.int/biologicals/expert_committee/BS2326_FXII.pdf?ua=1

2. CAUTION

This preparation is not for administration to humans or animals in the human food chain.

The preparation contains material of human origin, and either the final product or the source materials, from which it is derived, have been tested and found negative for HBsAg, anti-HIV and HCV RNA. As with all materials of biological origin, this preparation should be regarded as potentially hazardous to health. It should be used and discarded according to your own laboratory's safety procedures. Such safety procedures should include the wearing of protective gloves and avoiding the generation of aerosols. Care should be exercised in opening ampoules or vials, to avoid cuts.

3. UNITAGE

The standard was assayed in an international collaborative study. The units assigned to this preparation are:

Factor XI Functional activity (FXI:C): 0.71 IU/ampoule
Factor XI Antigen (FXI:Ag): 0.78 IU/ampoule
Factor XII Functional activity (FXII:C): 0.86 IU/ampoule
Factor XII Antigen (FXII:Ag): 0.80 IU/ampoule

Results from 29 laboratories employing one-stage clotting assays were used to value assign functional activity (FXI:C) to the 2nd IS relative to the 1st IS. The FXI antigen value (FXI:Ag) was assigned relative to local normal pooled plasma (total number of donors >20,000) by ELISA method, using data from 11 laboratories.
For FXII, results from 20 laboratories using one-stage clotting assays were used to value assign functional activity (FXII:C) relative to local normal plasma pools (number of donors 566). The FXII antigen value (FXII:Ag) was also assigned relative to local normal plasma pools (216 donors), using results from 8 laboratories using ELISA methods.

Uncertainty: the assigned unitage does not carry an uncertainty associated with its calibration. The uncertainty may therefore be considered to be the variance of the ampoule content which was determined to be +/- 0.25 %.

4. CONTENTS

Country of origin of biological material: United Kingdom.

The material was prepared from a plasma pool derived from normal healthy donors (United Kingdom National Blood Transfusion Service). Blood was collected into CPD-adenine anticoagulant and subjected to two centrifugation steps after which the plasma was frozen rapidly and stored at -70ºC until the day of ampoule filling. Individual donations were tested and found negative for HBsAg, anti-HIV-1/2 and anti-HCV. The material was formulated with glycine and a buffering agent HEPES (N-[2-Hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid) at a final concentration of 1 % w:v and 40 mmol/L respectively. To avoid activation of FXI/FXII, polyethylene vessels were used for storage and transport of the pooled plasma. The frozen pooled plasma was thawed at 37ºC and maintained at room temperature throughout the process. The material was filled into siliconised glass ampoules and freeze dried under conditions used for International Biologicals Standards (1).
Activation status of the material: The non-activated partial thromboplastin time (NAPTT) is known to be sensitive to activated clotting factor especially factor XIa and so it was used to assess the activation status of the finished product. The long mean clotting time of 300s (n = 9; sd ± 2.26) for 15/180 indicates the samples to be relatively unactivated.

5. STORAGE

Unopened ampoules should be stored in the dark below -20ºC
Please note: because of the inherent stability of lyophilized material, NIBSC may ship these materials at ambient temperature.

6. DIRECTIONS FOR OPENING

DIN ampoules have an 'easy-open' coloured stress point, where the narrow ampoule stem joins the wider ampoule body. Various types of ampoule breaker are available commercially. To open the ampoule, tap the ampoule gently to collect material at the bottom (labelled) end and follow manufactures instructions provided with the ampoule breaker.

7. USE OF MATERIAL

No attempt should be made to weigh out any portion of the freeze-dried material prior to reconstitution
Allow ampoules to warm to room temperature. Open ampoule, taking care to ensure that all material is in the lower part, and reconstitute with 1.0 mL of distilled water. After reconstitution please store the material as indicated in section 8 (On Bench Stability).

8. STABILITY

Reference materials are held at NIBSC within assured, temperature-controlled storage facilities. Reference Materials should be stored on receipt as indicated on the label.

NIBSC follows the policy of WHO with respect to its reference material. It is the policy of WHO not to assign expiry dates to international reference materials. They remain valid with the assigned potency and status until withdrawn or amended. Accelerated degradation studies, which involve potency estimation of ampoules stored at elevated temperatures relative to ampoules stored at below -150°C, has indicated that the Standard is stable when stored at - 20° or below.

On Bench Stability: It is recommended that assays are to be performed as soon as possible after reconstitution. The stability of coagulation factors in plasma standards, after reconstitution, is mainly affected by two components - the surface of the container and the storage temperature. Unlike other WHO IS for blood coagulation factors it is recommended that upon reconstitution, the standard should either be transferred to a plastic tube or retained in the siliconised ampoule at room temperature (18 - 22 ºC) in order to prevent cold activation of FXI or FXII. Results from NIBSC indicated no significant change in FXI or FXII clotting activity or antigen measurement when the reconstituted material was stored at room temperature in the siliconised ampoules for over 3 hours. However, users

will be advised that local validation will be necessary if the reconstituted standard is stored under different conditions. The use of frozen aliquots of this International Standard cannot be recommended since the effect of freezing and thawing, under local conditions, on the FXI or FXII activity is unpredictable.

9. REFERENCES

1. Campbell PJ (1974) J Biol Standardization, 2, 249-267

10. ACKNOWLEDGEMENTS

The participants of the study.

11. FURTHER INFORMATION

Further information can be obtained as follows;
This material: enquiries@nibsc.org
WHO Biological Standards:
http://www.who.int/biologicals/en/
JCTLM Higher order reference materials:
http://www.bipm.org/en/committees/jc/jctlm/
Derivation of International Units:
http://www.nibsc.org/standardisation/international_standards.aspx
Ordering standards from NIBSC:
http://www.nibsc.org/products/ordering.aspx
NIBSC Terms & Conditions:
http://www.nibsc.org/terms_and_conditions.aspx

12. CUSTOMER FEEDBACK

Customers are encouraged to provide feedback on the suitability or use of the material provided or other aspects of our service. Please send any comments to enquiries@nibsc.org

13. CITATION

In all publications, including data sheets, in which this material is referenced, it is important that the preparation's title, its status, the NIBSC code number, and the name and address of NIBSC are cited and cited correctly.

14. MATERIAL SAFETY SHEET

Classification in accordance with Directive 2000/54/EC, Regulation (EC) No 1272/2008: Not applicable or not classified

Physical and Chemical properties			
Physical appearance: Freeze-dried powder		Corrosive:	No
Stable:	Yes	Oxidising:	No
Hygroscopic:	No	Irritant:	Yes
Flammable:	No	Handling:See caution, Section 2	
Other (specify):	Contains material of human origin		

Toxicological properties	
Effects of inhalation:	Not established, avoid inhalation
Effects of ingestion:	Not established, avoid ingestion
Effects of skin absorption:	Not established, avoid contact with skin

Suggested First Aid	
Inhalation:	Seek medical advice
Ingestion:	Seek medical advice
Contact with eyes:	Wash with copious amounts of water. Seek medical advice
Contact with skin:	Wash thoroughly with water.

Action on Spillage and Method of Disposal
Spillage of ampoule contents should be taken up with absorbent material wetted with an appropriate disinfectant. Rinse area with an appropriate disinfectant followed by water. Absorbent materials used to treat spillage should be treated as biological waste.

15. LIABILITY AND LOSS

In the event that this document is translated into another language, the English language version shall prevail in the event of any inconsistencies between the documents.
Unless expressly stated otherwise by NIBSC, NIBSC's Standard Terms and Conditions for the Supply of Materials (available at http://www.nibsc.org/About_Us/Terms_and_Conditions.aspx or upon request by the Recipient) ("Conditions") apply to the exclusion of all other terms and are hereby incorporated into this document by reference. The Recipient's attention is drawn in particular to the provisions of clause 11 of the Conditions.

16. INFORMATION FOR CUSTOMS USE ONLY

Country of origin for customs purposes*: United Kingdom * Defined as the country where the goods have been produced and/or sufficiently processed to be classed as originating from the country of supply, for example a change of state such as freeze-drying.
Net weight: ~100 mg
Toxicity Statement: Toxicity not assessed
Veterinary certificate or other statement if applicable**.** **Attached:** No

17. CERTIFICATE OF ANALYSIS

NIBSC does not provide a Certificate of Analysis for WHO Biological Reference Materials because they are internationally recognised primary reference materials fully described in the instructions for use. The reference materials are established according to the WHO Recommendations for the preparation, characterization and establishment of international and other biological reference standards http://www.who.int/bloodproducts/publications/TRS932Annex2_Inter_biolefstandardsrev2004.pdf (revised 2004). They are officially endorsed by the WHO Expert Committee on Biological Standardization (ECBS) based on the report of the international collaborative study which established their suitability for the intended use.