Medicines & Healthcare products Regulatory Agency

NIBSC Confidence in Biological Medicines

WHO International Standard
1st International Standard for Activated Factor IX (FIXa), Human
Established 1999
NIBSC code: 97/562
Instructions for use
(Version 4.0, Dated 10/02/2014)

1. INTENDED USE

The 1st International Standard for Activated Factor IX (FIXa), Human, coded 97/562 consists of ampoules containing aliquots of a freeze-dried purified human FIXa prepared from activated recombinant human Factor IX. This preparation was established as the 1st International Standard for Activated Factor IX, Human, by the Expert Committee on Biological Standardisation of the World Health Organisation in October 1999

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 potency of the 1st International Standard for FIXa was calibrated by 9 laboratories from 8 different countries against the NIBSC reference preparation, 92/720 by chromogenic and clotting methods specific for FIXa. The assigned potency of this preparation is

11.0 IU/ampoule.

The unit of FIXa as defined by this standard is not identical to a unit of purified Factor IX when fully activated. Studies are in progress to determine the exact relationship between the unit of FIXa as defined by this standard and the International Unit of Factor IX.

4. CONTENTS

Country of origin of biological material: USA.

Thirty-one ml of frozen activated recombinant human Factor IX (activated by Factor XIa) were thawed at 37°C and then diluted with approximately 3.5 litres of 0.05M Tris, 0.15M NaCl, 5 mg/ml Trehalose, 1.25% human albumin, pH 7.4. The solution was distributed at 4°C into 3500 ampoules, coded 97/562. The mean residual moisture content was 0.025%. The mean weight of liquid content of 69 check weight ampoules was 1.0072g, with coefficient of variation 0.15%. The contents of the ampoules were then freeze-dried under the conditions normally used for international biological standards.

5. STORAGE

Unopened ampoules should be stored in the dark at or below –20°C. Allow ampoules to warm to room temperature.
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

Open ampoule, taking care to ensure that all material is in the lower part, and reconstitute with 1.0ml distilled water. The reconstituted Standard should be used as soon as possible.

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 materials. It is the policy of WHO not to assign an expiry date to their international reference materials. They remain valid with the assigned potency and status until withdrawn or amended.

Accelerated degradation study, which involves potency estimation of ampoules stored at elevated temperatures relative to ampoules stored at below -150°C, of 97/562 showed that after 10 years storage, no detectable sign of degradation was observed in samples stored at -20°C or below. The predicted loss for Standard stored at +20°C was 0.8% per year and this supports shipment at ambient temperature. These studiesshown that when stored at -20°C or below the assigned value remain valid until the material is replacem or withdrawn. The accelerated degradation study and real time monitoring will continue for the lifetime of the standard.

Users who have data supporting any deterioration in the characteristics of any reference preparation are encouraged to contact NIBSC.

On bench stability: Studies on stability after reconstitution showed that no detectable sign of degradation was observed in samples stored on melting ice for 4 hours. However, when stored at room temperature (+22°C) after reconstitution, up to 20% and 25 % loss of activity were observed after 2 and 4 hours respectively. It is recommended that once reconstituted, the standard should be kept on melting ice, in plastic tube for no longer than 4 hours.

9. REFERENCES

Campbell PJ. Procedures used for the production of biological standards and reference preparations. J Biol Standardisation. 1974, 2, 259-267.

10. ACKNOWLEDGEMENTS

All participants in the international collaborative study. We are grateful to Genetics Institute, Andover, Massachussetts, USA for supply of candidate materials for the collaborative study. We also thank Dr K Mertens, CLB, Sanquin Blood Supply Foundation, The Netherlands, for his pre- and post-collaborative study investigation.

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:

National Institute for Biological Standards and Control,
Potters Bar, Hertfordshire, EN6 3QG. T +44 (0)1707 641000, nibsc.org
WHO International Laboratory for Biological Standards,
UK Official Medicines Control Laboratory

World Health Organization

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 solid	Corrosive: No
Stable: Yes	Oxidising: No
Hygroscopic: Yes	Irritant: Yes
Flammable: No	Handling: See caution, Section 2
Other (specify): derived material	Contains recombinant and human plasma
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: ~50 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.