Medicines & Healthcare products Regulatory Agency

NIBSC Confidence in Biological Medicines

WHO Reference Reagent
Activin A (Human, Recombinant)
NIBSC code: 91/626
Instructions for use
(Version 5.0, Dated 23/01/2008)

1. INTENDED USE

This consists of a batch of ampoules (coded 91/626) containing recombinant DNA-derived human Activin A analysed by international collaborative study and established as the First WHO Reference Reagent for Activin A by the Expert Committee on Biological Standardization of the World Health Organisation (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 assigned potency is 5 U per ampoule where, for the purposes of this preparation 1 U is approximately equivalent to 1 microgram.

4. CONTENTS

Country of origin of biological material: United Kingdom.
Each ampoule contains the residue after freeze-drying of 1ml of a solution that contained:

NaCl	8.8mg
HSA	5.0mg
Tris	6.0mg
Trehalose	2.0mg
rec Activin A	

5. STORAGE

Unopened ampoules should be stored at -20°C.
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

For practical purposes each ampoule contains the same quantity of activin A. The entire content of each ampoule should be completely dissolved in an accurately measured amount of buffer solution. No attempt should be made to weigh out portions of the freeze dried powder. The use of water to reconstitute ampoule contents is not recommended.The material has not been sterilized and the ampoules contain no bacteriostat.

8. PREPARATION OF AMPOULES

8.1 Bulk material

Highly purified recombinant activin A was kindly donated to WHO by Genentech Inc., 460 Point San Bruno Boulevard, South San Francisco, CA 94080, USA.

8.2 Distribution into ampoules

The preparation was received as a solution of recombinant human activin (0.5 mg/ml in 0.15M NaCl/0.05M TRIS, pH 7.5). Twenty ml of this solution were diluted to a final volume of 200ml with a buffer containing 0.5% (w/v) purified, peptidase-free human plasma albumin, 0.2%(w/v) trehalose, 50mM TRIS and 0.15M NaCl. The solution was filtered (0.45µm) and further diluted with the same buffer to give a final volume of 2l. The solution was distributed into ampoules coded 91/626 with a filling volume of 1ml, lyophilised and sealed according to procedures described by WHO for International Biological Standards (2) and stored at -20°C in the dark.

9. COLLABORATIVE STUDY

The preparation in ampoules coded 91/626 was evaluated by international collaborative study in which four laboratories from three countries took part. Assays contributed included in vitro assays based upon FSH stimulation or anti-proliferative effects, and immunoassays for total and free activin. The study was designed to:-

- compare, by bioassay and immunoassay, the ampouled preparation of recombinant activin A with local standards presently in use.
- calibrate the preparation of activin A for use as a WHO Reference Reagent.
- assess the stability of the proposed Reference Reagent after accelerated thermal degradation.

9.1 Activity of ampoule contents

The candidate material was found to be active in all assays contributed to the study with a potency relative to the local standards of 1.12 (GCV 32%) based on a nominal ampoule content of 5µg. The preparation coded 91/626 was established as the First Reference Reagent for Activin A, human, recombinant, with a defined ampoule content of 5 IU per ampoule where, for the purposes of this preparation,1IU is approximately equivalent to 1microgram.

10. STABILITY

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.

Reference materials are held at NIBSC within assured, temperature-controlled storage facilities. Reference Materials should be stored on receipt as indicated on the label. For information specific to a particular biological standard, contact standards@nibsc.ac.uk.

In addition, once reconstituted, diluted or aliquoted, users should determine the stability of the material according to their own method of preparation, storage and use.

NIBSC follows the policy of WHO with respect to its reference materials.

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

The ampouled preparation 91/626 appears to be sufficiently stable to serve as a Reference Reagent since the predicted yearly loss of activity in ampoules stored at -20°C is less than 0.1%.

11. REFERENCES

1. WHO Technical Report Series No.897, 2000
2. WHO Technical Report Series No.800, 1990; 181-214

12. ACKNOWLEDGEMENTS

We gratefully acknowledge the important contributions of all the participants, Genentech Inc. who kindly donated the recombinant activin A and CBRM for preparation of the ampouled materials.

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WHO International Laboratory for Biological Standards,
UK Official Medicines Control Laboratory

World Health Organization

13. 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

14. 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

15. 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.

16. 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: white lyophilised powder	Corrosive: No
Stable: Yes	Oxidising: No
Hygroscopic: Yes	Irritant: No
Flammable: No	Handling: See caution, Section 2
Other (specify): Contains material of human origin. Can react with oxidising materials. Avoid contact with acids and	
Toxicological properties	
Effects of inhalation: No adverse effects have been reported for this material	
Effects of ingestion: No adverse effects have been reported for this material	
Effects of skin absorption: No adverse effects have been reported for this material	
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.	

17. 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.

18. 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: 22mg
Toxicity Statement: Non-toxic
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.