Medicines & Healthcare products Regulatory Agency

NIBSC Confidence in Biological Medicines

WHO International Standard
Follicle-Stimulating Hormone and Luteinizing Hormone, Human, Urinary, For Bioassay
NIBSC code: 10/286
Instructions for use
(Version 3.0, Dated 03/04/2013)

1. INTENDED USE

The 4th International Standard (IS) for human, urinary Follicle-Stimulating hormone (FSH) and Luteinizing Hormone (LH) in ampoules coded 98/704, was established in 2000 and has been widely used for the calibration, by *in vivo* bioassay, of preparations with FSH and LH bioactivities of human, urinary origin. The WHO Expert Committee on Biological Standardization (ECBS) has recognized (2011) the need for a replacement IS for the assignment of potency to therapeutic preparations containing human, urinary FSH and LH bioactivities used in the treatment of infertility. The 5th IS, coded 10/286, was established at the 63rd meeting of the ECBS in 2012. This material replaces the 4th IS which is discontinued.

The 5th IS, in ampoules coded 10/286, contains purified proteins of human, urinary origin for the value assignment of FSH and LH bioactivities in preparations of human, urinary origin by *in vivo* bioassay, only.

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

Each ampoule contains 183 INTERNATIONAL UNITS of FSH bioactivity and 177 INTERNATIONAL UNITS of LH bioactivity.

4. CONTENTS

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

Purified proteins from human menopausal urine*	approx.58µg
Human serum albumin	0.2 % (w/v)
Lactose	0.5 % (w/v)

* Human chorionic gonadotrophin, derived from human menopausal urine or added exogenously during manufacture will contribute to the LH bioactivity defined above.

5. STORAGE

Unopened ampoules should be stored at -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
For practical purposes, each ampoule contains the same quantity of material. The entire content of each ampoule should be completely dissolved in an accurately measured amount of buffer solution. The use of water to reconstitute ampoule contents is not recommended. The material has not been sterilized and the ampoules contain no bacteriostat.

COLLABORATIVE STUDY
The preparation was evaluated in a collaborative study in which eleven laboratories in ten countries took part, organized with the following aims:

1) To calibrate the candidate preparation,10/286 relative to the 4th IS (98/704) for FSH and LH bioactivities by *in vivo* bioassays.
2) To assess the suitability of the candidate preparation 10/286 to serve as the 5th IS for the calibration of therapeutic preparations of human, urinary origin containing FSH and LH bioactivities by bioassay.
3) To determine the stability of the candidate preparation 10/286 by comparison with ampoules stored at elevated temperatures as part of an accelerated degradation stability study.

The geometric mean potency calculated from all laboratories using $\log_{10}$(organ weight) as the assay response was 183 IU FSH bioactivity per ampoule (n = 10; 95% confidence limits 165-202; GCV 15%) and 177 IU LH bioactivity per ampoule (n = 9; 95% confidence limits 159-197; GCV 15%).

The candidate preparation 10/286 is sufficiently stable to serve as an IS. Analysis of the thermally accelerated degradation samples in this study gave a predicted 0.001% loss of potency per year for FSH when stored at -20°C, but no consistent loss of activity was detected for the samples stored at +20°C or +37°C for LH. This suggests that 10/286 is likely to be highly stable under long term storage at -20°C.

8. 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.

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

9. REFERENCES

10. ACKNOWLEDGEMENTS

We gratefully acknowledge the important contributions of all the participants in the collaborative study and Instituto Massone S.A. and IBSA Institut Biochimique S.A. for the kind donation of the bulk material.

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

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

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 white 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		

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: 7mg
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.