Medicines & Healthcare products Regulatory Agency

NIBSC Confidence in Biological Medicines

**WHO International Standard**
**WHO 1st International Standard for C1-inhibitor, concentrate**
**NIBSC code: 08/256**
**Instructions for use**
**(Version 2.0, Dated 28/10/2010)**

## 1. INTENDED USE

The 1st International Standard for C1-inhibitor, concentrate (08/256) was established by the Expert Committee on Biological Standardisation of the World Health Organisation (WHO) in October 2010. The intended use of this preparation is to calibrate the measurement of functional C1-inhibitor in products derived from human plasma used in replacement therapy. 08/256 has not been evaluated for the potency estimation of recombinant products.

## 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 C1-inhibitor, concentrate (08/256) was determined by functional assay, relative to local normal plasma pools, in a collaborative study that involved 28 laboratories from 13 different countries.

The assigned potency of this preparation is: 9.6 IU/ ampoule

## 4. CONTENTS

Country of origin of biological material: United Kingdom.
One manufacturer generously provided 100,000 U (200 vials) of their C1-inhibitor product as the source material. Each vial contained 500 U of a freeze-dried preparation, purified from pooled human plasma. The material was reconstituted and diluted to a final concentration of 10 U/ml (based on the labelled potency) in 10 mM HEPES buffer (pH 7.4) containing 0.15 M sodium chloride and 5 mg/ml human albumin. A total of 9890 5 ml DIN ampoules were filled with 1 ml aliquots of the diluted material, with a mean filling weight of 1.0053 g (cv = 0.15%). Freeze drying was done following WHO procedures, to produce ampoules with a mean dry weight of 0.0236 g (cv = 5.17%) and a residual moisture of 0.2089% (cv = 27.53%).

## 5. STORAGE

Upon receipt unopened ampoules should be stored in the dark at or 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 the ampoule to reach ambient temperature before opening and reconstitute with 1.0 ml distilled water.

## 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.

To provide predictions on the long term stability of 08/256 the C1-inhibitor potency of ampoules stored under accelerated degradation conditions is being monitored over time. After one year little or no potency loss was observed for samples stored up to +56ºC.

Based on the results of a stability test, it is advised that samples are stored on wet ice following reconstitution, and potency assays should be completed within 4 hours of reconstitution.

## 9. REFERENCES

A report of the collaborative study to calibrate the standard is available from WHO, reference number WHO/BS/10.2144.

## 10. ACKNOWLEDGEMENTS

We are grateful to all the participants that took part in the collaborative study, to CSL Behring (Germany) and Sanquin (the Netherlands) for providing candidate materials, and to the Plasma Kallikrein-Kinin System Subcommittee of the Standardization and Scientific Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH).

## 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

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

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 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** |
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| 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.<br>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<br>* 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:** 23.6 mg |
| **Toxicity Statement:** Toxicity not assessed |
| **Veterinary certificate or other statement** if applicable**.**<br>**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.