WHO International Standard
1st International Standard for TNF receptor II Fc fusion protein (Etanercept, Human rDNA derived)
NIBSC code: 13/204

1. INTENDED USE
The World Health Organization (WHO) Expert Committee on Biological Standardization (ECBS) recognised the need for a reference standard to control biological assays used in the evaluation of TNF receptor II Fc fusion protein (etanercept). The preparation 13/204 was evaluated in an international collaborative study (described in section 3), and formally adopted by ECBS as the 1st WHO International Standard for in vitro biological activity of etanercept.

The standard can serve to control the performance of biological assays for etanercept and to support the establishment of in-house bioassay standards.

It should be noted that the bioassay unitage is not intended for describing the labelling or dosage of etanercept.

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 preparation has been assigned a unitage of 10,000 IU of biological activity per ampoule. This unit does not consider the inhibitory activity of the protein against Tumor necrosis factor-α (TNF-α) and is independent of the amount of TNF-α used in various assay systems.

Since the protein is an inhibitor of TNF-α, the inhibitory activity of the standard has been established in a cytotoxicity assay using the L929 (murine fibroblast) cell line. Based on ED50 responses from data of nine laboratories, 2.4 IU of this reference standard inhibits the cytotoxic effect of 10-20 IU of 3rd IS for TNF-α (coded 12/154) in L929 cytotoxicity assays.

As the inhibitory activity may vary according to the assay format, users should establish a relationship between the units assigned to the WHO international standard, and the unitage assigned to the in-house standard in the assay system being used. Users should also note that the biological activity of TNF-α is also likely to vary between different suppliers and this should be controlled by use of an appropriate standard (e.g. WHO IS).

The preparation was tested in a collaborative study involving 28 laboratories in 15 countries. Participants were asked to assay the candidate preparation using assay systems established in house, and to report results. Data were returned for cytotoxicity, apoptosis, reporter gene and binding assays. (see reference in section 9, WHO/BS/2015.2257)

4. CONTENTS
Country of origin of biological material: United Kingdom.

National Institute for Biological Standards and Control
Porton Down, Salisbury, SP4 0JG
Tel: (01722) 718200, nibsc.org
WHO International Laboratory for Biological Standards
UK Official Medicines Control Laboratory
collaborative study for their contribution in evaluating the candidate preparations.

11. FURTHER INFORMATION

Further information can be obtained as follows:

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

<table>
<thead>
<tr>
<th>Physical and Chemical properties</th>
<th>Physical and Chemical properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classification in accordance with Directive 2000/54/EC, Regulation (EC) No 1272/2008: Not applicable or not</td>
<td>Corrosive: No</td>
</tr>
<tr>
<td>Stable: Yes</td>
<td>Oxidising: No</td>
</tr>
<tr>
<td>Hygroscopic: No</td>
<td>Irritating: No</td>
</tr>
<tr>
<td>Flammable: No</td>
<td>Handling: See caution, Section 2</td>
</tr>
<tr>
<td>Other (specify): Contains material of human origin</td>
<td></td>
</tr>
</tbody>
</table>

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: 4.6g
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_biolrefstandardsrev2004.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.