



**WHO International Standard  
Somatotropin (Recombinant DNA-Derived Human Growth Hormone)  
NIBSC code: 98/574  
Instructions for use  
(Version 5.0, Dated 07/03/2018)**

## 1. INTENDED USE

The 2nd International standard for somatotropin consists of a batch of ampoules containing lyophilised somatotropin (recombinant DNA-derived growth hormone) plus excipients, coded 98/574. The material was ampouled under identical conditions to the first international standard for somatotropin, (88/624), and was evaluated and calibrated in an international collaborative study by comparison with the 1st IS. At its 51st meeting, in 2001, the Expert Committee on Biological Standardization of WHO established the preparation as the 2nd International Standard for somatotropin.

## 2. CAUTION

**This preparation is not for administration to humans or animals in the human food chain.**

The material is not of human or bovine origin. 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

1.95 mg per ampoule (total somatotropin protein, including higher molecular weight forms and related impurities)

3.0 International units per mg Somatotropin

Uncertainty: The International Unit of 98/574 is assigned without uncertainty. Where required, the uncertainty of the ampoule content of 98/574 may be considered to be the coefficient of variation of the fill volume, which was determined to be 0.07%.

As with the previous standard (88/624) users should recognise that the % of somatotropin is not defined. The active form of the molecule is generally considered to be the monomer, determined by size-exclusion HPLC. Since the exact percentage of monomer may depend on the specific assay method employed, the figure of 1.95mg/ampoule should therefore be corrected for % monomer, determined using the method practised in the user's laboratory. For calibration of bioassay methods, the figure of 3.0IU/mg also relates to somatotropin monomer, which should again be independently determined.

## 4. CONTENTS

Country of origin of biological material: United Kingdom.

Each ampoule contains the freeze dried residue of 1ml of solution which contained:

Somatropin (rec.DNA human growth hormone)	
Glycine	20mg
Mannitol	2mg
Lactose	2mg
Sodium Bicarbonate	2.5mg

## 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 all practical purposes each ampoule contains the same amount of the above materials. Dissolve the total contents in a known amount of suitable buffer solution with carrier protein (free of peptidase), where extensive dilution is required, to minimise loss by surface adsorption. No attempt should be made to weigh out portions of the freeze-dried powder.

For economy of use it is recommended that the solution be subdivided into several small containers, which are frozen rapidly to below -70 C and then stored below -30°C in the dark. Repeated freezing and thawing should be avoided.

The material has not been sterilized and contains no bacteriostat.

## 8. CHARACTERISATION AND PROPERTIES OF THE STANDARD

### 8.1 Bulk Material

Bulk Somatotropin was generously donated by Novo Nordisk, through the good offices of Dr Anne Munk Jespersen. The preparation was supplied with a certificate of analysis showing the material to be consistent with current pharmaceutical grades of somatotropin.

### 8.2 Preparation Of Ampoules

Ampoules were prepared according to procedures used for the preparation of WHO International Standards. Bulk somatotropin (20g) was dissolved in carrier solution (see section 3) to give a 10 X concentrate. This was filtered through a 0.45u filter, diluted to a final volume of 10l with carrier solution, and distributed in 10 000 x 1ml aliquots into neutral glass ampoules. After lyophilisation the ampoules were sealed under nitrogen by heat fusion.

For the fill 98/574, the recorded parameters were:

Mean solution weight: 1.0088g/ampoule

Relative standard deviation: 0.07%

Residual moisture: 0.66%

Relative standard deviation 6.5%

### 8.3 Collaborative Study

The preparation was evaluated by international collaborative study (16 laboratories, 9 countries), designed with the following aims:

i) to determine the suitability of the preparation to serve as the International Standard for somatotropin by studying its performance in the current range of physico-chemical and biological assay methods employed for somatotropin

ii) to assign a content in terms of the existing (1st) International Standard for somatotropin, using the currently recognized assay procedure (SE HPLC)

iii) to confirm the specific biological activity of the candidate preparation

iv) to confirm the stability of the candidate preparation



Estimates of content, in terms of the 1st IS, were in the range 1.80 - 2.08mg per ampoule.

Estimates of purity by size-exclusion HPLC (dimer + aggregates) were in the range 96-99%.

Estimates of purity by techniques resolving monomeric impurities (Reverse phase or ion-exchange chromatography, capillary zone electrophoresis) were in the range 96-100%.

The mean of all bioassay estimates (in vivo + in vitro) was 5.8IU per ampoule.

Upon storage at elevated temperatures, the preparation exhibited no degradation leading to the production of dimers or higher aggregates. Production of monomeric degradation products was observed, but the predicted rate of degradation at -20°C was 0.017% per year.

Based on these findings, and with the advice and agreement of participants, WHO established the preparation as the 2nd International Standard for somatotropin, with the formally assigned ampoule contents stated in section 4.

### 9. 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.

### 10. 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](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](http://www.nibsc.org/terms_and_conditions.aspx)

### 11. 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

### 12. 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.

### 13. 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 powder	Corrosive: No
Stable: Yes	Oxidising: No
Hygroscopic: Yes	Irritant: No
Flammable: No	Handling: See caution, Section 2
Other (specify):	
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.	

### 14. 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](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.

### 15. INFORMATION FOR CUSTOMS USE ONLY

<b>Country of origin for customs purposes*:</b> 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.
<b>Net weight:</b> 27mg
<b>Toxicity Statement:</b> Non-toxic
<b>Veterinary certificate or other statement</b> if applicable. <b>Attached:</b> 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\\_biologicalstandardsrev2004.pdf](http://www.who.int/bloodproducts/publications/TRS932Annex2_Inter_biologicalstandardsrev2004.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.