Medicines & Healthcare products Regulatory Agency

NIBSC Confidence in Biological Medicines

WHO International Standard
1st International Standard For Alpha-1-Antitrypsin, Plasma-Derived
NIBSC code: 05/162
Instructions for use
(Version 2.1, Dated 27/10/2009)

1. INTENDED USE

Alpha-1-Antitrypsin (AAT) belongs to the serpin (serine proteinase inhibitor) family of inhibitors and elastase is the main physiological target. Plasma-derived therapeutic AAT products are used to treat AAT deficiency (Alpha-1), a genetic disorder identified in virtually all populations that can cause liver and lung disease in adults and children. The 1st International Standard for AAT is made from AAT purified from plasma, was provided by a manufacturer of therapeutic concentrates and is intended primarily for use to standardise the determination of potencies of AAT used for replacement therapy including plasma-derived, recombinant and transgenic products. The standard is also suitable for assigning total protein and antigen concentrations to AAT preparations. For antigen determinations individual laboratories should investigate the suitability of the antibody used for the material to be tested. This is particularly important when recombinant products are being tested where differences in glycosylation patterns may affect the results. Reports of the studies are available as BS working documents WHO/BS/06.2044, and WHO/BS/08.2092.

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 AAT was determined as part of a collaborative study where the inhibitory activity of AAT was determined by titration against trypsin. The molar concentration of active trypsin was determined by active site titration using 4-Nitrophenyl 4-guanidinobenzoate hydrochloride (NPGB). AAT and trypsin form a tight 1:1 stoichiometric complex so titration of AAT against a known concentration of trypsin allows expression of active AAT concentration in molar units. The concentration of active AAT in this International Standard is 243 nmoles per ampoule. The total protein and antigen concentration of the standard was also determined, using a number of methods including amino acid analysis, and found to be consistent with the active concentration. This is equivalent to 12.4 mg AAT per ampoule applying a molecular weight of 51 000 g/mole, determined by mass spectrometry for this preparation. Recombinant preparations with different molecular weights will require a different conversion factor to calculate the mg amount from moles of active inhibitor of the recombinant preparation determined in titration assays which include this Standard. International Standards are traditionally assigned units based on consensus values and represent the primary standard for a particular measurand and as such are not assigned an uncertainty. The uncertainty of the ampoule content of 05/162 may be considered as the coefficient of variation of the fill which was 0.15%

4. CONTENTS

Country of origin of biological material: United Kingdom.

After reconstitution each ampoule will contain, in addition to active AAT, phosphate buffer and saline (17 mM phosphate; 38 mM chloride, 81 mM sodium at pH 7.0) and 144 mM mannitol added as a bulking agent. No other proteins were added. A total of 9792 ampoules of 05/162 were prepared with a mean filling weight of 1.0057 g (cv = 0.15 %), a mean dry weight of 0.0468 g (cv = 3.74 %) and residual moisture of 0.6615 % (cv = 11.31 %).

5. STORAGE

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 aterial prior to reconstitution
This International Standard is intended to be a primary reference material for local calibrators and should not be used as a reagent. Ampoules should be stored at -20 °C or below (but are shipped at ambient temperatures and are stable for short periods). Before use, the ampoules should be warmed to room temperature and the contents of the ampoule should be reconstituted in 1 ml of distilled water and stored on ice for use within the same day.

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.

9. REFERENCES

10. ACKNOWLEDGEMENTS

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.

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

World Health Organization

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: White powder	Corrosive: No
Stable: Yes	Oxidising: No
Hygroscopic: No	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: 10mg
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_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.