PUBLIC HEALTH COMMITTEE
EUROPEAN PHARMACOPOEIA COMMISSION
GROUP OF EXPERTS NO. 6B
(HUMAN BLOOD AND BLOOD PRODUCTS)

CONCENTRATUM ANTI-HAEMOPHILICUM HUMANUM CRYODESIOGATUM
Human Antihaemophilic Factor Concentrate Freeze-dried

Distribution
For action:
- Members of Group of Experts No. 6B (Human Blood and Blood Products)

Strasbourg
60.742
03.53

* Under the aegis of the Public Health Committee (Partial Agreement)
CONCENTRATUM ANTI-HAEMOPHILICUM HUMANUM CRYODESICCatum
Human Antihaemophilic Factor Concentrate Freeze-dried

1. Human antihaemophilic factor concentrate is a freeze-dried preparation containing the coagulation factor VIII obtained from human plasma or from human antihaemophilic cryoprecipitate from donors satisfying the requirements prescribed in the monograph on Sanguis Humanus (Vol. III, page 344).

6. It may be prepared for example by extraction of the cryoprecipitate or the cryoethanol precipitate with buffer and fractionation by a non denaturing precipitate- or chromatographic-system.

9. After sterilisation by filtration the final solution is distributed into its final sterile glass containers in a manner so as to ensure freedom from microbiological contamination and immediately frozen. It is subsequently freeze-dried and the containers are sealed in vacuo or under nitrogen. No preservative is added during or after preparation.

14. When dissolved in the volume of water for injections stated on the label, the solution contains not less than 10 international Units of factor VIII activity per ml. The specific activity of the preparation is not less than 0.5 International Units per mg of protein.

19. A white or very pale yellow powder or friable solid.

IDENTIFICATION
21. Precipitation tests with species-specific antisera carried out on a freshly prepared solution in the volume of water for injections stated on the label show that the preparation contains only plasma proteins of human origin.

25. The assay for factor VIII serves also to identify the product.
Tests

1. pH (Vol. I, page 63). The pH of the reconstituted preparation is between 6.5 and 7.5.

2. Solubility. It dissolves completely under gentle stirring within 5 minutes at 25°C. The solution does not become more than 0.1% opalescent at 25°C. The solution is stable at 4°C for at least 6 months.

3. Hemagglutination. Anti-A and anti-B. The reconstituted preparation diluted 1:100 with water to obtain volume 29, containing about 100 mg of protein, does not show the haemagglutination titre 24 hours after standing at 4°C, when titrated against 2 ml of a solution of 0.85% NaCl, 2 ml of a 7.5% solution of NaCl and 2 ml of a 2% solution of bovine serum albumin.

4. Reconstituted preparation, a volume equivalent to at least 6 International Units, for each mouse and 60 International Units for each guinea-pig.

5. Stability. The reconstituted preparation is stable at 2°C to 25°C for at least 6 months.


8. Analysed for N, C, H, O, P and S. The results are as follows: N, 9.2%; C, 14.5%; H, 4.0%; O, 40.0%; P, 0.2%; S, 0.3%.


10. In the test for toxins, the solution is kept at 2°C to 25°C for 4 hours. If the solution is kept at 2°C to 25°C for 4 hours, the solution is not opalescent at 25°C.

11. In the test for sterility, the reconstituted preparation is injected into mice and guinea-pigs. The results are as follows: mice, 60 International Units; guinea-pigs, 60 International Units.

12. Assay. (Vol. II, page 53) The assay consists of injecting a volume equivalent to at least 10 International Units per kg of body weight into the tail vein or subcutaneously.

13. In the test for purity, the reconstituted preparation is injected into mice and guinea-pigs.


15. Stability. The reconstituted preparation is stable at 2°C to 25°C for at least 6 months.


18. Analysed for N, C, H, O, P and S. The results are as follows: N, 9.2%; C, 14.5%; H, 4.0%; O, 40.0%; P, 0.2%; S, 0.3%.

19. Assay. (Vol. II, page 53) The assay consists of injecting a volume equivalent to at least 10 International Units per kg of body weight into the tail vein or subcutaneously.

20. In the test for toxins, the solution is kept at 2°C to 25°C for 4 hours. If the solution is kept at 2°C to 25°C for 4 hours, the solution is not opalescent at 25°C.


23. Analysed for N, C, H, O, P and S. The results are as follows: N, 9.2%; C, 14.5%; H, 4.0%; O, 40.0%; P, 0.2%; S, 0.3%.


25. In the test for toxins, the solution is kept at 2°C to 25°C for 4 hours. If the solution is kept at 2°C to 25°C for 4 hours, the solution is not opalescent at 25°C.


28. Analysed for N, C, H, O, P and S. The results are as follows: N, 9.2%; C, 14.5%; H, 4.0%; O, 40.0%; P, 0.2%; S, 0.3%.

29. Assay. (Vol. II, page 53) The assay consists of injecting a volume equivalent to at least 10 International Units per kg of body weight into the tail vein or subcutaneously.

30. In the test for toxins, the solution is kept at 2°C to 25°C for 4 hours. If the solution is kept at 2°C to 25°C for 4 hours, the solution is not opalescent at 25°C.


33. Analysed for N, C, H, O, P and S. The results are as follows: N, 9.2%; C, 14.5%; H, 4.0%; O, 40.0%; P, 0.2%; S, 0.3%.

34. Assay. (Vol. II, page 53) The assay consists of injecting a volume equivalent to at least 10 International Units per kg of body weight into the tail vein or subcutaneously.

35. In the test for toxins, the solution is kept at 2°C to 25°C for 4 hours. If the solution is kept at 2°C to 25°C for 4 hours, the solution is not opalescent at 25°C.


38. Analysed for N, C, H, O, P and S. The results are as follows: N, 9.2%; C, 14.5%; H, 4.0%; O, 40.0%; P, 0.2%; S, 0.3%.

39. Assay. (Vol. II, page 53) The assay consists of injecting a volume equivalent to at least 10 International Units per kg of body weight into the tail vein or subcutaneously.

40. In the test for toxins, the solution is kept at 2°C to 25°C for 4 hours. If the solution is kept at 2°C to 25°C for 4 hours, the solution is not opalescent at 25°C.
ASSAY

Estimate the factor VIII activity using the two-stage method (Vol. , page ). A single-stage method may be used if it has been shown to give identical results to those obtained using the two-stage method, using the International Standard for Blood Coagulation Factor VIII (I) Concentrate as the standard.

STORAGE

Store protected from light at a temperature below 10° under vacuum or in an atmosphere of nitrogen in sterile containers sealed so as to exclude micro-organisms and moisture.

Expiration date When stored under the prescribed conditions it may be used up to 2 years from the date of the estimation of activity.

LABELLING

The labelling complies with the relevant national legislation and international agreements.

In addition the label on the container and the label on the package indicate:

- the amount of factor VIII in International Units in the container
- the volume of water for injections to be used to reconstitute the preparation
- that the preparation must be used immediately after reconstitution
- that the reconstituted solution should not be used if solution is incomplete or if a clot forms.

The label on the container or a leaflet included in the package indicates:

- that the contents must be used on one occasion only
- the name and quantity of any added substance

(1) The equivalence in International Units of factor VIII of the International Standard is stated from time to time by the World Health Organisation.