The stated potency is not less than 100 IU/ml. The estimated potency is not less than the stated potency. The confidence limits (P = 0.95) of the estimated potency are not less than 80 per cent and not more than 125 per cent.

STORAGE

See *Human normal immunoglobulin (0338)*.

LABELLING

See *Human normal immunoglobulin (0338)*.

The label states the number of International Units per container.

01/2008:1528

HUMAN VARICELLA IMMUNOGLOBULIN FOR INTRAVENOUS ADMINISTRATION

Immunoglobulinum humanum varicellae ad usum intravenosum

DEFINITION

Human varicella immunoglobulin for intravenous administration is a liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G. It is obtained from plasma from selected donors having antibodies against human herpesvirus 3 (varicella-zoster virus 1). *Human normal immunoglobulin for intravenous administration (0918)* may be added.

It complies with the monograph on *Human normal immunoglobulin for intravenous administration (0918)*, except for the minimum number of donors, the minimum total protein content and the limit for osmolality.

POTENCY

The potency is determined by comparing the antibody titre of the immunoglobulin to be examined with that of a reference preparation calibrated in International Units, using an immunoassay of suitable sensitivity and specificity (*2.7.1*).

The International Unit is the activity contained in a stated amount of the International Standard for anti varicella-zoster immunoglobulin. The equivalence in International Units of the International Standard is stated by the World Health Organisation.

The stated potency is not less than 25 IU/ml. The estimated potency is not less than the stated potency. The confidence limits (P = 0.95) of the estimated potency are not less than 80 per cent and not more than 125 per cent.

STORAGE

See *Human normal immunoglobulin for intravenous administration (0918)*.

LABELLING

See *Human normal immunoglobulin for intravenous administration (0918)*.

The label states the number of International Units per container.

01/2008:2298

HUMAN VON WILLEBRAND FACTOR

Factor humanus von Willebrandi

DEFINITION

Human von Willebrand factor is a preparation of a plasma protein fraction that contains the glycoprotein von Willebrand factor with varying amounts of coagulation factor VIII, depending on the method of preparation. It is prepared from human plasma that complies with the monograph on *Human plasma for fractionation (0853)*.

This monograph applies to preparations formulated according to the von Willebrand factor activity.

The potency of the preparation, reconstituted as stated on the label, is not less than 20 IU of von Willebrand factor per millilitre.

PRODUCTION

The method of preparation includes steps that have been shown to remove or to inactivate known agents of infection; if substances are used for the inactivation of viruses, the subsequent purification procedure must be validated to demonstrate that the concentration of these substances is reduced to a suitable level and that any residues are such as not to compromise the safety of the preparation for patients.

The specific activity is not less than 1 IU of von Willebrand factor per milligram of total protein before the addition of any protein stabiliser.

The von Willebrand factor fraction is dissolved in a suitable liquid. Excipients such as a stabiliser may be added. No antimicrobial preservative is added. The solution is passed through a bacteria-retentive filter, distributed aseptically into the final containers and immediately frozen. It is subsequently freeze-dried and the containers are closed under vacuum or under an inert gas.

VALIDATION STUDIES

COMPOSITION. It shall be demonstrated that the manufacturing process yields a product having a consistent composition with respect to von Willebrand factor, factor VIII and the proportions of von Willebrand factor and factor VIII.

von Willebrand factor multimers. The distribution of the different von Willebrand factor multimers is determined by a suitable method such as sodium dodecyl sulphate (SDS) agarose gel electrophoresis with or without Western blot analysis, using a suitable normal human plasma as standard. Visualisation of the multimeric pattern may be performed using, for example, an immunoenzymatic technique and quantitative evaluation may be carried out by densitometric analysis.

von Willebrand factor activity (*2.7.21*). The von Willebrand factor activity is estimated by determining the ristocetin cofactor activity and by one or more other suitable assays such as determination of collagen-binding activity using a suitable reference preparation.

von Willebrand factor activity/antigen ratio. Consistency of the manufacturing process with respect to the ratio of von Willebrand factor activity to von Willebrand factor antigen content is demonstrated.

PRODUCTS THAT SHOW PARTICLES AFTER RECONSTITUTION. If a few particles remain when the preparation is reconstituted, it shall be demonstrated during validation studies that the potency is not significantly affected after passage of the preparation through the filter to be provided with the preparation.

CHARACTERS

Appearance: white or pale yellow, hygroscopic powder or friable solid.

Reconstitute the preparation to be examined as stated on the label immediately before carrying out the identification, tests (except those for solubility and water) and assay.

IDENTIFICATION

The assay for von Willebrand factor serves also to identify the preparation.

TESTS

Solubility. To a container of the preparation to be examined add the volume of the solvent stated on the label at the recommended temperature. The preparation dissolves completely with gentle swirling within 10 min, giving a clear or slightly opalescent, colourless or slightly yellow solution.

In addition, where the label states that the product may show a few particles after reconstitution, reconstitute the preparation as described on the label and pass it through the filter provided: the filtered solution is clear or slightly opalescent.

pH (*2.2.3*): 6.5 to 7.5.

Osmolality (*2.2.35*): minimum 240 mosmol/kg.

Total protein. If necessary, dilute an accurately measured volume of the preparation to be examined with a 9 g/l solution of *sodium chloride R*, to obtain a solution that may be expected to contain about 15 mg of protein in 2 ml. Place 2.0 ml of this solution in a round-bottomed centrifuge tube and add 2 ml of a 75 g/l solution of *sodium molybdate R* and 2 ml of a mixture of 1 volume of *nitrogen-free sulphuric acid R* and 30 volumes of *water R*. Shake, centrifuge for 5 min, decant the supernatant liquid and allow the inverted tube to drain on filter paper. Determine the nitrogen in the residue by the method of sulphuric acid digestion (*2.5.9*) and calculate the amount of protein by multiplying the result by 6.25. *For some products, especially those without a protein stabiliser, this method may not be applicable. Another validated method for protein determination must therefore be performed.*

Anti-A and anti-B haemagglutinins (*2.6.20*). Dilute the preparation to be examined with a 9 g/l solution of *sodium chloride R* to contain 6 IU of von Willebrand factor activity per millilitre. The 1 to 64 dilutions do not show agglutination.

Water. Determined by a suitable method, such as the semi-micro determination of water (*2.5.12*), loss on drying (*2.2.32*) or near infrared spectrophotometry (*2.2.40*), the water content is within the limits approved by the competent authority.

Sterility (*2.6.1*). It complies with the test for sterility.

Pyrogens (*2.6.8*). It complies with the test for pyrogens. Inject per kilogram of the rabbit's mass a volume of the preparation to be examined equivalent to not less than 100 IU of von Willebrand factor activity.

ASSAY

von Willebrand factor (*2.7.21*). The estimated potency is not less than 80 per cent and not more than 120 per cent of the stated potency. The confidence limits (P = 0.95) are not less than 80 per cent and not more than 120 per cent of the estimated potency.

Pending the availability of an International Standard for von Willebrand factor concentrate calibrated for use in the collagen-binding assay, only the ristocetin cofactor assay may be used.

Factor VIII (*2.7.4*). The assay is carried out where the factor VIII content is greater than 10 IU of factor VIII per 100 IU of von Willebrand factor activity. The estimated potency is not less than 60 per cent and not more than 140 per cent of the stated potency. The confidence limits (P = 0.95) are not less than 80 per cent and not more than 120 per cent of the estimated potency.

STORAGE

In an airtight container, protected from light.

LABELLING

The label states:

- the number of International Units of von Willebrand factor in the container;
- the number of International Units of factor VIII in the container, or that the content of factor VIII is less than or equal to 10 IU of factor VIII per 100 IU of von Willebrand factor activity;
- the amount of protein in the container;
- the name and quantity of any added substance;
- the name and volume of the liquid to be used for reconstitution;
- where applicable, that the preparation may show the presence of a few particles after reconstitution;
- that the transmission of infectious agents cannot be totally excluded when medicinal products prepared from human blood or plasma are administered.

01/2008:0912

HYALURONIDASE

Hyaluronidasum

[9001-54-1]

DEFINITION

Hyaluronidase is an enzyme extracted from mammalian testes (for example bovine testes) and capable of hydrolysing mucopolysaccharides of the hyaluronic acid type. It contains not less than 300 IU of hyaluronidase activity per milligram, calculated with reference to the dried substance. It may contain a suitable stabiliser.

PRODUCTION

The animals from which hyaluronidase is derived must fulfil the requirements for the health of animals suitable for human consumption.

CHARACTERS

A white or yellowish-white, amorphous powder, soluble in water, practically insoluble in acetone and in ethanol.