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HUMAN PLASMA (POOLED AND TREATED FOR VIRUS INACTIVATION)

Plasma humanum coagmentatum conditumque ad exstinguendum virum

DEFINITION

Human plasma (pooled and treated for virus inactivation) is a frozen or freeze-dried, sterile, non-pyrogenic preparation obtained from human plasma derived from donors belonging to the same ABO blood group. The preparation is thawed or reconstituted before use to give a solution for infusion.

The human plasma used complies with the monograph Human plasma for fractionation (0853) .

PRODUCTION

The units of plasma to be used are cooled to −30 °C or lower within 6 h of separation of cells and always within 24 h of collection.

The pool is prepared by mixing units of plasma belonging to the same ABO blood group.

The pool of plasma is tested for hepatitis B surface antigen (HBsAg) and for HIV antibodies using test methods of suitable sensitivity and specificity; the pool must give negative results in these tests.

Hepatitis A virus RNA. The plasma pool is tested using a validated nucleic acid amplification technique (2.6.21). A positive control with 1.0×10^2 IU of hepatitis A virus RNA per millilitre and, to test for inhibitors, an internal control prepared by addition of a suitable marker to a sample of the plasma pool are included in the test. The test is invalid if the positive control is non-reactive or if the result obtained with the internal control indicates the presence of inhibitors. The pool complies with the test if it is found non-reactive for hepatitis A virus RNA.

Hepatitis C virus RNA. The plasma pool is tested using a validated nucleic acid amplification technique (2.6.21). A positive control with 1.0×10^2 IU of hepatitis C virus RNA per millilitre and, to test for inhibitors, an internal control prepared by addition of a suitable marker to a sample of the plasma pool are included in the test. The test is invalid if the positive control is non-reactive or if the result obtained with the internal control indicates the presence of inhibitors. The pool complies with the test if it is found non-reactive for hepatitis C virus RNA.

Hepatitis C virus RNA for NAT testing BRP is suitable for use as a positive control.

To limit the potential burden of B19 virus in plasma pools, the plasma pool is also tested for B19 virus using a validated nucleic acid amplification technique (2.6.21).

B19 virus DNA. The plasma pool contains not more than 10.0 IU/µL.

A positive control with 10.0 IU of B19 virus DNA per microlitre and, to test for inhibitors, an internal control prepared by addition of a suitable marker to a sample of the plasma pool are included in the test. The test is invalid if the positive control is non-reactive or if the result obtained with the internal control indicates the presence of inhibitors.

B19 virus DNA for NAT testing BRP is suitable for use as a positive control.

The method of preparation is designed to minimise activation of any coagulation factor (to minimise potential thrombogenicity) and includes a step or steps that have been shown to inactivate known agents of infection; if substances are used for the inactivation of viruses during production, 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.

Inactivation process. The solvent-detergent process, which is one of the methods used to inactivate enveloped viruses, uses treatment with a combination of tributyl phosphate and octoxinol 10; these reagents are subsequently removed by oil extraction or by solid phase extraction so that the amount in the final product is less than 2 µg/mL for tributyl phosphate and less than 5 µg/mL for octoxinol 10.

No antimicrobial preservative is added.

The solution is passed through a bacteria-retentive filter, distributed aseptically into the final containers and immediately frozen; it may subsequently be freeze-dried.

Plastic containers comply with the requirements for sterile plastic containers for human blood and blood components (3.2.3).

Glass containers comply with the requirements for glass containers for pharmaceutical use (3.2.1).

CHARACTERS

The frozen preparation, after thawing, is a clear or slightly opalescent liquid free from solid and gelatinous particles. The freeze-dried preparation is an almost white or slightly yellow powder or friable solid.

Thaw or reconstitute the preparation to be examined as stated on the label immediately before carrying out the identification, tests and assay.

IDENTIFICATION

A. Examine by electrophoresis (2.2.31) comparing with normal human plasma. The electropherograms show the same bands.

B. It complies with the test for anti-A and anti-B haemagglutinins (see Tests).

TESTS

pH (2.2.3): 6.5 to 7.6.

Osmolality (2.2.35): minimum 240 mosmol/kg.

Total protein: minimum 45 g/L.

Dilute with a 9 g/L solution of sodium chloride R to obtain a solution containing 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 sulfuric acid R and 30 volumes of water R. Shake, centrifuge for 5 min, decant the supernatant and allow the inverted tube to drain on filter paper. Determine the nitrogen in the residue by the method of sulfuric acid digestion (2.5.9) and calculate the quantity of protein by multiplying the result by 6.25.

Activated coagulation factors (2.6.22). It complies with the test for activated coagulation factors. Carry out the test with 0.1 mL of the preparation to be examined instead of 10-fold and 100-fold dilutions. The coagulation time for the preparation to be examined is not less than 150 s.

Anti-A and anti-B haemagglutinins (2.6.20). The presence of haemagglutinins (anti-A or anti-B) corresponds to the blood group stated on the label.

Hepatitis A virus antibodies: minimum 1.0 IU/mL, determined by a suitable immunochemical method (2.7.1).

Human hepatitis A immunoglobulin BRP is suitable for use as a reference preparation.

Irregular erythrocyte antibodies. The preparation to be examined does not show the presence of irregular erythrocyte antibodies when examined without dilution by an indirect antiglobulin test.

Citrate. Liquid chromatography (2.2.29).

Test solution. Dilute the preparation to be examined with an equal volume of a 9 g/L solution of sodium chloride R. Filter the solution using a filter with 0.45 µm pores.

Reference solution. Dissolve 0.300 g of sodium citrate R in water R and dilute to 100.0 mL with the same solvent.

Column:

— *size*: *l* = 0.3 m, Ø = 7.8 mm;

— *stationary phase*: cation exchange resin R (9 µm).

Mobile phase: 0.51 g/L solution of sulfuric acid R.

Flow rate: 0.5 mL/min.

Detection: spectrophotometer at 215 nm.

Equilibration: 15 min.

Injection: 10 µL.

Retention time: citrate = about 10 min.

Limit:

— *citrate*: maximum 25 mmol/L.

Calcium: maximum 5.0 mmol/L.

Atomic absorption spectrometry (2.2.23, Method I).

Source: calcium hollow-cathode lamp using a transmission band preferably of 0.5 nm.

Wavelength: 622 nm.

Atomisation device: air-acetylene or acetylene-propane flame.

Potassium: maximum 5.0 mmol/L.

Atomic emission spectrometry (2.2.22, Method I).

Wavelength: 766.5 nm.

Sodium: maximum ►200◄ mmol/L.

Atomic emission spectrometry (2.2.22, Method I).

Wavelength: 589 nm.

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 spectrometry (2.2.40), the water content is within the limits approved by the competent authority (freeze-dried product).

Sterility (2.6.1). It complies with the test.

►**Pyrogens (2.6.8) or Bacterial endotoxins (2.6.14)**. It complies with the test for pyrogens or, preferably and where justified and authorised, with a validated *in vitro* test such as the bacterial endotoxin test.

For the pyrogen test, inject 3 mL per kilogram of the rabbit's mass.

Where the bacterial endotoxin test is used, the preparation to be examined contains less than 0.1 IU of endotoxin per millilitre.
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ASSAY

Factor VIII. Carry out the assay of human coagulation factor VIII (2.7.4) using a reference plasma calibrated against the International Standard for blood coagulation factor VIII in plasma.

The estimated potency is not less than 0.5 IU/mL. The confidence limits (P = 0.95) are not less than 80 per cent and not more than 120 per cent of the estimated potency.

Factor V. Carry out the assay of human coagulation factor V described below using a reference plasma calibrated against the International Standard for blood coagulation factor V in plasma.

Using imidazole buffer solution pH 7.3 R, prepare at least 3 two-fold dilutions of the preparation to be examined, preferably in duplicate, from 1 in 10 to 1 in 40. Test each dilution as follows: mix 1 volume of plasma substrate deficient in factor V R, 1 volume of the dilution to be examined, 1 volume of thromboplastin R and 1 volume of a 3.5 g/L solution of calcium chloride R; measure the coagulation times, i.e. the interval between the moment at which the calcium chloride solution is added and the 1st indication of the formation of fibrin, which may be observed visually or by means of a suitable apparatus.

In the same manner, determine the coagulation time of 4 twofold dilutions (1 in 10 to 1 in 80) of human normal plasma in imidazole buffer solution pH 7.3 R.

Check the validity of the assay and calculate the potency of the test preparation by the usual statistical methods (for example, 5.3).

The estimated potency is not less than 0.5 IU/mL. The confidence limits (P = 0.95) are not less than 80 per cent and not more than 120 per cent of the estimated potency.

Factor XI. Carry out the assay of human coagulation factor XI (2.7.22) using a reference plasma calibrated against the International Standard for blood coagulation factor XI in plasma.

The estimated potency is not less than 0.5 IU/mL. The confidence limits (P = 0.95) are not less than 80 per cent and not more than 125 per cent of the estimated potency.

Protein C. Carry out the assay of human protein C (2.7.30) using a reference plasma calibrated against the International Standard for human protein C in plasma.

The estimated potency is not less than 0.7 IU/mL. The confidence limits (P = 0.95) are not less than 80 per cent and not more than 120 per cent of the estimated potency.

Protein S. Carry out the assay of human protein S (2.7.31) using a reference plasma calibrated against the International Standard for human protein S in plasma.

The estimated potency is within the limits approved for the particular product. The confidence limits (P = 0.95) are not less than 80 per cent and not more than 120 per cent of the estimated potency.

Plasmin inhibitor (α_2-antiplasmin). Carry out the assay of human plasmin inhibitor (2.7.25) using a reference plasma calibrated against human normal plasma.

1 unit of human plasmin inhibitor is equal to the activity of 1 mL of human normal plasma. Human normal plasma is prepared by pooling plasma units from not fewer than 30 donors and storing at −30 °C or lower.

The estimated potency is not less than 0.2 units/mL. The confidence limits (P = 0.95) are not less than 80 per cent and not more than 120 per cent of the estimated potency.

LABELLING

The label states:

— the ABO blood group;

— the method used for virus inactivation.