MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION

GPHARMACOPOEIA MONOGRAPH

Von Willebrand factor	**PM.3.3.2.0005.15** First Edition

The present Pharmacopoeia Monograph applies to von Willebrand factor preparations, which are a protein fraction of human plasma containing the glycoprotein von Willebrand factor along with a varying amount of human coagulation factor VIII. Von Willebrand factor preparations contain no preservatives and no antibiotics.

MANUFACTURE

Plasma obtained from healthy donors and corresponding to the requirements of the Pharmacopoeia Monograph “Human plasma for fractionation” should be used for the manufacture of von Willebrand factor preparations.

The manufacturing technology includes stages to eliminate or inactivate infectious pathogens. If any chemical compounds are used to inactivate viruses during the manufacturing process, their concentration should be decreased to a level that does not affect the safety of the medicinal product for patients. The manufacturing method should ensure that obtained products have constant concentrations of von Willebrand factor, blood coagulation VIII factor, and a constant ratio of these factors. The manufacturing procedure should ensure that the obtained product has a characteristic distribution of various von Willebrand factor polymers and a constant ratio of the von Willebrand factor activity and the von Willebrand factor antigen content. No antimicrobial preservatives are used in the manufacturing process.

The activity of von Willebrand factor in the medicinal product should be not

less than 1 IU per milligramme of protein before any protein stabilizers are added.

The medicinal product solution is packaged in primary containers using sterilizing filtration technique, freeze-dried, and closed under a vacuum or in an inert gas atmosphere.

TESTS

Description. The medicinal product is an amorphous hygroscopic cake appearing as a white to pale yellow tablet or powder (unless different requirements are included in the Normative Document). The test is carried out by visual examination.

Identification

Species specificity. Identity is confirmed by the presence of only human serum proteins. The test is carried out by gel immunoelectrophoresis, using sera against human, bovine, horse, and porcine serum proteins, as described in the General Pharmacopoeia Monograph “Agarose gel immunoelectrophoresis”. This test may also be performed with the gel immunodiffusion method, in accordance with the General Pharmacopoeia Monograph “Gel immunodiffusion”. The test should produce precipitation lines only with the serum against human serum proteins.

Von Willebrand factor. Demonstrated by the presence of von Willebrand factor activity. The test is carried out by agglutination or with the enzyme immunoassay method, in accordance with the General Pharmacopoeia Monograph “Determination of blood coagulation factor activity”.

Note

If albumin or similar stabilizers are included in the medicinal product, their identity should be tested.

Reconstitution time. Not more than 10 minutes (unless otherwise specified in the Normative Document). A description of the method should be included, along with the solvent used, its volume, and the dissolution conditions (solvent temperature, need for mixing, etc.).

Water content. Not more than 2 %. The test is carried out with the Karl Fischer method, in accordance with the General Pharmacopoeia Monograph "Determination of water" (unless otherwise specified in the Normative Document). The test method and the sample size necessary for the tests should be specified in the Normative Document.

Particulate matter. Visible particulate matter should be absent in the reconstituted solution. The test is carried out in accordance with the General Pharmacopoeia Monograph "Visible particulate matter in medicinal products for parenteral use and ophthalmic dosage forms". The Normative Document should include the name of the solvent, a description of the reconstitution technique, and whether the product has to be filtered through a supplied filter.

pH value. From 6.5 to 7.5. The test is carried out by potentiometry, in accordance with the General Pharmacopoeia Monograph "Ionometry".

Osmolality. Not less than 240 mOsmol/kg. The test is carried out in accordance with the General Pharmacopoeia Monograph "Osmolarity".

Protein content. The content of protein per vial or millilitre of reconstituted solution should be specified in the Normative Document. The test is carried out in accordance with the General Pharmacopoeia Monograph "Determination of protein".

Anti-A and anti-B haemagglutinins. No agglutination should be observed at the 1:64 dilution of the medicinal product. The test is carried out in accordance with the General Pharmacopoeia Monograph "Determination of anti-A and anti-B haemagglutinins in medicinal products containing human immunoglobulins".

Note.

Preparation of the tested sample. The reconstituted medicinal product is diluted with 0.9 % sodium chloride solution or with a buffer low-ionic strength solution (LISS) to a von Willebrand factor content of 6 IU/mL.

Von Willebrand factor activity. Not less than 20 IU per millilitre of reconstituted solution. The test is carried out by agglutination or with the enzyme immunoassay method, in accordance with the General Pharmacopoeia Monograph "Determination of blood coagulation factor activity".

Human coagulation factor VIII activity. The coagulation factor VIII activity, calculated per vial or per millilitre of reconstituted solution, should be specified in the Normative Document. Factor VIII activity should be determined when its content in the medicinal product exceeds 10 IU of factor VIII per 100 IU of von Willebrand factor activity.

The test is carried out with the chromogenic method or by coagulometry, in accordance with the General Pharmacopoeia Monograph “Determination of blood coagulation factor activity”.

Stabilizer(s). The stabilizer(s) added to the medicinal product is / are quantified using the methods described in the General Pharmacopoeia Monograph “Gas chromatography” and / or in accordance with the General Pharmacopoeia Monograph “High-performance liquid chromatography (HPLC)” (unless a different method is specified in the Normative Document). Acceptable limits for the content of stabilizer(s) should be specified in the Normative Document.

Virus-inactivating agents. The residual content of virus-inactivating agent(s) in the medicinal product is quantified using the methods described in the General Pharmacopoeia Monograph “Gas chromatography” and / or in accordance with the General Pharmacopoeia Monograph “High-performance liquid chromatography (HPLC)” (unless a different method is specified in the Normative Document). Acceptable limits for the content of virus-inactivating agent(s) should be specified in the Normative Document.

Sterility. The medicinal product is required to be sterile. The test is carried out in accordance with the General Pharmacopoeia Monograph “Sterility”.

Pyrogenicity or **Bacterial endotoxins.** The medicinal product is required to be non-pyrogenic, or its content of bacterial endotoxins should be not more than 0.05 EU per 1 IU of von Willebrand factor activity.

The test is carried out in accordance with the General Pharmacopoeia Monograph “Pyrogenicity” (not less than 100 IU of von Willebrand factor per kilogramme of animal body weight; the administered volume of the medicinal product should not exceed 1 mL per kilogramme of animal body weight), or this

test may be carried out in accordance with the General Pharmacopoeia Monograph “Bacterial endotoxins”, using the method described in the Normative Document.

Viral safety

Hepatitis B virus surface antigen (HBsAg). The medicinal product should contain no hepatitis B virus surface antigen. The test is carried out by enzyme immunoassay, using test systems approved for use in Russian health care practice and having a sensitivity not less than 0.1 IU/mL according to the Instructions for Use.

Anti-hepatitis C virus antibodies. The medicinal product should contain no anti-hepatitis C virus antibodies. The test is carried out by enzyme immunoassay, using test systems approved for use in Russian health care practice and having 100 % sensitivity and specificity according to the Instructions for Use.

Anti-human immunodeficiency virus (HIV-1 and HIV-2) antibodies and HIV-1 p24 antigen. The medicinal product should contain no anti-human immunodeficiency virus (HIV-1 and HIV-2) antibodies and no HIV-1 p24 antigen. The test is carried out by enzyme immunoassay, using test systems approved for use in Russian health care practice and having 100 % sensitivity and specificity according to the Instructions for Use.

Packaging and Labeling. In accordance with the General Pharmacopoeia Monograph “Medicinal products containing human plasma”.

Storage. The medicinal product should be stored away from light, in the temperature range of 2 to 8 °C, unless otherwise specified in the Normative Document.