MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION

PHARMACOPOEIA MONOGRAPH

Human coagulation factor IX **PM.3.3.2.0004.15**
First Edition

The present Pharmacopoeia Monograph applies to human coagulation factor IX preparations obtained from human plasma for fractionation.

Human coagulation factor IX is a preparation of the protein fraction of human blood obtained from plasma for fractionation using a method that effectively isolates coagulation factor IX from other factors of the prothrombin complex (II, VII, X).

The medicinal product, after being reconstituted under the conditions specified on the label, should have an activity of not less than 20 IU of factor IX per millilitre.

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 human coagulation factor IX 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 medicinal product may contain stabilizers (albumin, antithrombin III, polysorbate 80, sodium chloride, sodium citrate, glycine, etc.). Specific activity (not less than 50 IU/mg for total protein) should be determined before adding any stabilizing protein.

No antimicrobial preservatives may be used during the manufacturing pro-

cedure. 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. A white to pale yellow powder or loose solid substance (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.

Factor IX. Demonstrated by the presence of factor IX activity. The test is carried out by coagulometry or in the chromogenic method, in accordance with the General Pharmacopoeia Monograph "Determination of blood coagulation factor activity".

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. 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 (if necessary) the tested product preparation procedure.

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 using an appropriate method, in accordance with the General Pharmacopoeia Monograph "Determination of protein".

Coagulation factor IX activity. Coagulation factor IX activity, per vial or millilitre of reconstituted solution, should be specified in the Normative Document. 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".

Activated coagulation factors. The coagulation time of the 1:10 and 1:100 dilutions of the medicinal product should be not less than 150 seconds. The test is carried out 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 0.3 EU per 1 IU of coagulation factor IX.

The test is carried out in accordance with the General Pharmacopoeia Monograph “Pyrogenicity” (not less than 50 IU of coagulation factor IX per kilogramme of animal body weight) or 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.