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14. Dutton RP, *et al.* Factor VIIa for correction of traumatic coagulopathy. *J Trauma* 2004; **57:** 709–18.
15. Levi M, *et al.* Efficacy and safety of recombinant factor VIIa for treatment of severe bleeding: a systematic review. *Crit Care Med* 2005; **33:** 883–90.

Preparations

Ph. Eur.: Human Coagulation Factor VII.

Proprietary Preparations (details are given in Part 3)
Arg.: NovoSeven; ***Austral.:*** NovoSeven; ***Austria:*** NovoSeven; ***Belg.:*** NovoSeven; ***Braz.:*** NovoSeven; ***Canad.:*** NiaStase; ***Chile:*** NovoSeven; ***Cz.:*** NovoSeven; ***Denm.:*** NovoSeven; ***Fin.:*** NovoSeven; ***Fr.:*** NovoSeven; ***Ger.:*** NovoSeven; ***Gr.:*** NovoSeven; ***Hong Kong:*** NovoSeven; ***Hung.:*** NovoSeven; ***Irl.:*** NovoSeven; ***Israel:*** NovoSeven; ***Ital.:*** NovoSeven; Provertin-UM TIM 3; ***Jpn:*** NovoSeven; ***Malaysia:*** NovoSeven; ***Mex.:*** NovoSeven; ***Neth.:*** NovoSeven; ***Norw.:*** NovoSeven; ***NZ:*** NovoSeven; ***Philipp.:*** NovoSeven; ***Pol.:*** NovoSeven; ***Port.:*** NovoSeven; ***Rus.:*** NovoSeven (НовоСвен); ***S.Afr.:*** NovoSeven; ***Singapore:*** NovoSeven; ***Spain:*** NovoSeven; ***Swed.:*** NovoSeven; ***Switz.:*** NovoSeven; ***Thai.:*** NovoSeven; ***Turk.:*** NovoSeven; ***UK:*** NovoSeven; ***USA:*** NovoSeven.

Factor VIII

AHF; Antihaemophilic Factor; Facteur VIII.
ATC — B02BD02.
ATC Vet — QB02BD02.

Description. Factor VIII is a plasma protein involved in blood coagulation. It may be obtained from human plasma or produced by recombinant DNA technology. The names Moroctocog Alfa (see below) and Octocog Alfa (see below) are in use for recombinant factor VIII.

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Human Coagulation Factor VIII; Factor VIII Coagulationis Humanus; Dried Factor VIII Fraction BP 2008). A plasma protein fraction that contains the glycoprotein coagulation factor VIII with varying amounts of von Willebrand factor, depending on the method of preparation. It is prepared from human plasma obtained from blood from healthy donors; the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. The method of preparation includes a step or steps that have been shown to remove or inactivate known agents of infection. The factor VIII fraction is dissolved in an appropriate liquid, passed through a bacteria-retentive filter, distributed aseptically into the final containers, and immediately frozen. The preparation is freeze-dried and the containers sealed under vacuum or under an inert gas. Auxiliary substances such as a stabiliser may be added. No antimicrobial preservative is added. The specific activity is not less than 1 international unit of factor VIII:C per mg of total protein before the addition of any protein stabiliser. When reconstituted as stated on the label the resulting solution contains not less than 20 international units of factor VIII:C per mL.
A white or pale yellow hygroscopic powder or friable solid. Store in airtight containers. Protect from light.

Ph. Eur. 6.2 (Human Coagulation Factor VIII (rDNA); Factor VIII Coagulationis Humanus (ADNr)Dried Factor VIII (rDNA) BP 2008). A freeze-dried preparation of glycoproteins having the same activity as coagulation factor VIII in human plasma. It is prepared as full-length factor VIII (octocog alfa), or as a shortened two-chain structure (relative molecular mass 90 000 and 80 000), in which the B-domain has been deleted from the heavy chain (moroctocog alfa). Full-length human rDNA coagulation factor VIII contains 25 potential *N*-glycosylation sites, 19 in the B-domain of the heavy chain, 3 in the remaining part of the heavy chain (relative molecular mass 90 000) and 3 in the light chain (relative molecular mass 80 000).
Human coagulation factor VIII (rDNA) is produced by recombinant DNA technology in mammalian cell culture. Auxiliary substances such as a stabiliser may be added. A white or slightly yellow powder or friable mass. pH of the reconstituted preparation is 6.5 to 7.5. Protect from light.

USP 31 (Antihemophilic Factor). A sterile freeze-dried powder containing the factor VIII fraction prepared from units of human venous plasma that have been tested for the absence of hepatitis B surface antigen, obtained from whole-blood donors and pooled; it may contain heparin sodium or sodium citrate. It contains not less than 100 units per g of protein. Unless otherwise specified it should be stored at 2° to 8° in hermetically-sealed containers. It should be used within 4 hours of reconstitution and should be administered with equipment that includes a filter.
A white or yellowish powder. On reconstitution it is opalescent with a slight blue tinge or is a yellowish liquid.

USP 31 (Cryoprecipitated Antihemophilic Factor). A sterile frozen concentrate of human antihaemophilic factor prepared from the cryoprotein fraction, rich in factor VIII, of human venous plasma obtained from suitable whole-blood donors from a single unit of plasma derived from whole blood or by plasmapheresis, collected and processed in a closed system. It contains no preservative. It has an average potency of not less than 80 units per container. It should be stored at or below −18° in hermetically-sealed containers. It should be thawed to 20° to 37° before use; this liquid should be stored at room temperature and used within 6 hours of thawing; it should also be used within 4 hours of opening the container and administered with equipment that includes a filter.
A yellowish frozen solid. On thawing it becomes a very viscous, yellow, gummy liquid.

Moroctocog Alfa *(BAN, rINN)*

Moroctocogum Alfa; Moroktokog Alfa; Moroktokogialfa. (1—742)–(1637—1648)-Blood-coagulation factor VIII (human reduced) complex with 1649—2332-blood-coagulation factor VIII (human reduced).

Мороктоког Альфа

CAS — 284036-24-4.

Pharmacopoeias. *Eur.* (see p.vii) includes under the title Human Coagulation Factor VIII (rDNA) (see above).

Octocog Alfa *(BAN, rINN)*

Bay-w-6240; Factor VIII (rDNA); Octocogum Alfa. Blood-coagulation factor VIII (human), glycoform α.

Октоког Альфа

CAS — 139076-62-3;.

Pharmacopoeias. *Eur.* (see p.vii) includes under the title Human Coagulation Factor VIII (rDNA) (see above).

Units

The potency of factor VIII is expressed in international units and preparations may be assayed using the sixth International Standard for blood coagulation factor VIII concentrate, human (1998).

Adverse Effects and Precautions

Allergic reactions may sometimes follow the use of factor VIII preparations; the chills, urticaria, and headache experienced by some patients may be allergic manifestations. There is the possibility of intravascular haemolysis in patients with blood groups A, B, or AB receiving high doses or frequently repeated doses of factor VIII preparations due to the content of blood group isoagglutinins; also massive doses of some preparations may produce hyperfibrinogenaemia. Such risks should be reduced with more highly purified preparations.

Factor VIII preparations have been associated with the transmission of some viral infections, including hepatitis B and C, and more notably transmission of HIV. Strenuous efforts are now undertaken to screen the donor material from which factor VIII material is obtained and new methods of manufacture have also been introduced with the aim of inactivating any viruses present. Vaccination against hepatitis A and B is recommended for patients not already immune. Recombinant preparations are also available.

Some patients develop antibodies to factor VIII (see Resistance, below).

Effects on blood platelets. There have been case reports of thrombocytopenia associated with use of porcine factor VIII.[1] A retrospective study[2] of patients treated with porcine factor VIII found that the platelet count fell in 61% of 175 infusions given to 57 patients. The fall was generally clinically insignificant and platelet count appeared to recover within an hour. The effect was, however, dose-related, and larger reductions in platelet count were usually associated with intensive replacement over several days for surgery or trauma.

1. Green D, Tuite GF. Declining platelet counts and platelet aggregation during porcine VIII:C infusions. *Am J Med* 1989; **86:** 222–4.
2. Hay CRM, *et al.* Safety profile of porcine factor VIII and its use as hospital and home-therapy for patients with haemophilia-A and inhibitors: the results of an international survey. *Thromb Haemost* 1996; **75:** 25–9.

Resistance. Some patients with haemophilia A develop inhibitory antibodies to factor VIII (see Haemophilias, p.1048). The risk is highest within the first 20 to 100 treatments. Low-titre antibodies are usually transient and overcome by increased or continuing treatment with factor VIII. With high-titre highly responding antibodies, however, bleeding episodes may need to be managed with factor VIII inhibitor bypassing fraction (activated prothrombin complex concentrate), or recombinant factor VIIa. Highly responding antibodies can be eradicated by immune tolerance regimens, using regular infusion of factor concentrates over long periods, with additional immunosuppression and immuno-adsorption in some cases.[1] Postmarketing monitoring in Europe has revealed a higher number of cases of inhibitory antibodies associated with recombinant factor VIII preparations than would be expected from experience with plasma-derived products.[2] However, a review[3] by the EMEA found that, on the basis of available data, it was not possible to estimate and compare the incidence of inhibitors between different recombinant factor VIII products. They warned that recurrence of low-titre antibodies had occurred after switching from one product to another in previously treated patients with more than 100 exposure days who had a history of inhibitor development. They also requested that further investigation be undertaken by companies that market recombinant factor VIII products.

There have also been reports of lack of effect with the use of the recombinant factor VIII, moroctocog alfa, for prophylaxis, in patients who have no evidence of antibodies to factor VIII.[4]

1. Bolton-Maggs PHB, Pasi KJ. Haemophilias A and B. *Lancet* 2003; **361:** 1801–9.
2. EMEA. EMEA public statement: review of recombinant factor VIII (FVIII) products and inhibitor development: Advate, Kogenate Bayer/Helixate NexGen, Kogenate/Helixate, Recombinate, ReFacto (issued 18 October 2005). Available at: http://www.emea.europa.eu/pdfs/human/press/pus/33131605en.pdf (accessed 13/06/08)
3. EMEA. Public statement: EMEA completes the review of recombinant factor VIII products and inhibitor development (issued 31 July 2007). Available at: http://www.emea.europa.eu/pdfs/human/press/pus/31022507en.pdf (accessed 13/06/08)
4. Wyeth Canada. Important safety information about Refacto (moroctocog alfa), antihemophilic factor (recombinant) [BDDr-FVIII] (issued September 15, 2003). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/refacto_hpc-cps-eng.pdf (accessed 29/08/08)

Transmission of infections. Treatment with heat or chemicals and efforts to screen the donor material from which factor VIII and other clotting factors are obtained seem to have overcome problems with transmission of HIV and hepatitis B and C, although there is concern that non-lipid-enveloped viruses, such as human parvovirus B19 and hepatitis A, may still be transmitted. Vaccination against hepatitis A and B has been recommended for all patients who receive or may require blood products. Plasma-derived clotting factor preparations, or recombinant preparations containing added albumin, may carry a risk of transmission of variant Creutzfeldt-Jakob disease (see under Blood, p.1056). There has also been some concern about the use of human and animal products in the culture media used to manufacture recombinant clotting factor preparations, because of the theoretical risk of viral transmission from infected cell lines. Recombinant manufacturing techniques and formulations have changed over time and human and animal products are no longer used in some preparations.[1]

1. Keeling D, *et al.* United Kingdom Haemophilia Center Doctors' Organisation (UKHCDO). Guideline on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders. *Haemophilia* 2008; **14:** 671–84. Also available at: http://www.robsoft.plus.com/ukhcdo/docs/guidelines/2008_guideline_on_the_selection_and_use_of_therapeutic_products.pdf (accessed 13/08/08)

Pharmacokinetics

In patients with haemophilia A, factor VIII preparations have a terminal half-life of about 12 hours, whether human-derived or of recombinant origin.

◊ References.

1. Messori A, *et al.* Clinical pharmacokinetics of factor VIII in patients with classic haemophilia. *Clin Pharmacokinet* 1987; **13:** 365–80.
2. Björkman S, *et al.* Pharmacokinetics of factor VIII in humans: obtaining clinically relevant data from comparative studies. *Clin Pharmacokinet* 1992; **22:** 385–95.

Uses and Administration

Factor VIII is used as replacement therapy in patients with haemophilia A, a genetic deficiency of factor VIII; it may also be used in acquired haemophilia (see Haemophilias, p.1048).