ration of effect depends on the characteristics of the starch used; for 6% hetastarch the effect lasts for 24 to 36 hours.

Etherified starches are given intravenously as solutions in sodium chloride 0.9% or other electrolytes; concentrations used are usually 6 or 10%, although 3% solutions are also available for some. The dose and rate of infusion depend on the amount of fluid lost and degree of haemoconcentration; usual doses are in the range of 500 to 2500 mL daily, depending on the preparation used, and the infusion rate may be up to about 20 mL/kg per hour if necessary.

Hetastarch and pentastarch increase the erythrocyte sedimentation rate when added to whole blood. They are therefore used in leucapheresis procedures to increase the yield of granulocytes. Doses of 250 to 700 mL may be added to venous blood in the ratio 1 part to at least 8 parts of whole blood in such procedures. Up to 2 such procedures per week and a total of 7 to 10 have been reported to be safe.

Hetastarch and hexastarch have also been used in extracorporeal perfusion fluids.

◊ References.

1. Treib J, *et al.* An international view of hydroxyethyl starches. *Intensive Care Med* 1999; **25:** 258–68.

Administration in children. Etherified starches of various degrees of substitution and molecular weights have been used as plasma expanders in children.[1-4]

1. Boldt J, *et al.* Volume replacement with hydroxyethyl starch solutions in children. *Br J Anaesth* 1993; **70:** 661–5.
2. Brutocao D, *et al.* Comparison of hetastarch with albumin for postoperative volume expansion in children after cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 1996; **10:** 348–51.
3. Paul M, *et al.* A randomized, controlled study of fluid management in infants and toddlers during surgery: hydroxyethyl starch 6% (HES 70/0.5) vs lactated Ringer's solution. *Paediatr Anaesth* 2003; **13:** 603–8.
4. Liet J-M, *et al.* Plasma volume expansion by medium molecular weight hydroxyethyl starch in neonates: a pilot study. *Pediatr Crit Care Med* 2003; **4:** 305–7.

Stroke. Haemodilution with pentastarch has been tried in patients with acute ischaemic stroke (p.1185) in an attempt to improve reperfusion of the brain by lowering blood viscosity. However, one study was terminated early when an excess mortality was noted in the haemodilution group.[1] The early fatalities occurred almost exclusively in patients with severe strokes; cerebral oedema was the main cause of death within one week of the onset of symptoms. Among the survivors neurological recovery was better among those who received haemodilution. A systematic review[2] of 18 haemodilution studies, which included 5 using etherified starches, found no benefit in terms of fatality or functional outcome with haemodilution. See also Effects on the Blood, above

1. Hemodilution in Stroke Study Group. Hypervolemic hemodilution treatment of stroke: results of a randomized multicenter trial using pentastarch. *Stroke* 1989; **20:** 317–23.
2. Asplund K. Haemodilution for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 27/10/05).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Hemohes†; Hessico; Infukoll HES; Venofundin; Voluven; ***Austria:*** Elohast; Expafusin; Expahes; HAES-steril; Hyperhes; Isohes; Osmohes; Plasmasteril; Varihes; Voluven; ***Braz.:*** Pentaspan†; ***Canad.:*** Hextend; Pentaspan; ***Chile:*** HAES-steril; Hemohes; Voluven; ***Cz.:*** Elohast†; HAES-steril; Hemohes; HyperHAES; Serag-HAES; Tetraspan; Voluven; ***Denm.:*** HAES-steril; HyperHAES; Venofundin; Voluven; ***Fin.:*** HAES-steril; Hemohes; HyperHAES; Plasmafusin†; Venofundin; Voluven; ***Fr.:*** Heafusine†; Hesteril; Hyperhes; Voluven; ***Ger.:*** Expafusin; Haemofusin; HAES-Rheopond; HAES-steril; Hemohes; HyperHAES; Infukoll HES; Plasmafusin†; Plasmasteril†; Rheohes; Serag-HAES; Venofundin; Vitafusal; VitaHES; Voluven; ***Gr.:*** HAES-steril; Hemohes; Venofundin; Voluven; ***Hong Kong:*** Voluven; ***Hung.:*** HAES-steril; Hemohes; HyperHAES; Isohes†; Osmohes†; Tetraspan; Voluven; ***Indon.:*** Expafusin; Fima HES; HAES-steril; Hemohes; Voluven; WIDAHES; ***Israel:*** HAES-sterile; ***Ital.:*** Amidolite; HAES-steril; HyperHAES; Voluven; ***Jpn:*** Hespander; ***Malaysia:*** HAES-steril†; Voluven; ***Mex.:*** HAES-steril; Hestar; Pentaspan†; Voluven; ***Neth.:*** Elohaes; HAES-steril; Hemohes; HyperHAES; Venofundin; Voluven; ***Norw.:*** HAES-steril†; Hemohes; HyperHAES; Voluven; ***NZ:*** Hemohes; Pentaspan†; ***Philipp.:*** HAES-steril; Voluven; ***Pol.:*** HAES-steril; Hemohes; Voluven; ***Port.:*** HAES-steril; Hemohes; HyperHAES; Tetraspan; Venofundin; Voluven; ***Rus.:*** HAES-steril (ХАЕС-стерил); HyperHAES (ГиперХАЕС); Infukoll HES (Инфукол ГЭК); Refortan (Рефортан); Stabisol (Стабизол); Voluven (Волювен); ***S.Afr.:*** HAES-steril; Voluven; ***Singapore:*** HAES-steril; Hemohes†; ***Spain:*** Elohes; HAES Esteril; Hemohes; Hes Grifols; Hesteril; Voluven; ***Swed.:*** HAES-steril; Hemohes†; HyperHAES; Venofundin; Voluven; ***Switz.:*** Expahes†; HAES-steril; Hemohes; HyperHAES; Isohes†; Plasmasteril†; Varihes†; Venofundin; Voluven; ***Thai.:*** HAES-steril; Hemohes; Hespander†; Voluven; ***Turk.:*** Biohes; Bioplazma; Expahes; HAES-steril; Hemohes; Isohes; Plasmasteril; Varihes; Voluven; ***UK:*** Elohaes†; HAES-steril; Hemohes; HyperHAES; Infukoll; Venofundin; Volulyte; Voluven; ***USA:*** Hespan; Pentaspan; Voluven; ***Venez.:*** HAES-steril†.

Factor VII

Facteur VII; Proconvertin; SPCA; Stable Factor.

ATC — B02BD05.

ATC Vet — QB02BD05.

Description. Factor VII is a plasma protein involved in blood coagulation. It may be obtained from human plasma or produced by recombinant DNA technology. The name Eptacog Alfa (Activated) is in use for a recombinant factor VIIa.

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

Ph. Eur. 6.2 (Human Coagulation Factor VII; Factor VII Coagulationis Humanus; Dried Factor VII Fraction BP 2008). A plasma protein fraction that contains the single-chain glycoprotein factor VII and may also contain small amounts of the activated form, the two-chain derivative factor VIIa, as well as coagulation factors II, IX, and X, and protein C and protein S. 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 is designed to minimise activation of any coagulation factor and includes a step or steps that have been shown to remove or inactivate known agents of infection. The factor VII fraction is dissolved in a suitable 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. Heparin, antithrombin, and other auxiliary substances such as a stabiliser may be added. No antimicrobial preservative is added. The specific activity is not less than 2 international units of factor VII per mg of protein before the addition of any protein stabiliser. When reconstituted as stated on the label the resulting solution contains not less than 15 international units/mL.

A white or almost white, pale yellow, green, or blue hygroscopic powder or friable solid. Store in airtight containers. Protect from light.

Eptacog Alfa (Activated) *(BAN, rINN)*

Eptacog alfa (activado); Eptacog Alfa (activé); Eptacogum Alfa (activatum). Blood-coagulation factor VII (human clone λHVII2463 protein moiety).

Эптаког Альфа (Активированный)

CAS — 102786-52-7; 102786-61-8.

ATC — B02BD08.

ATC Vet — QB02BD08.

Units

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

The potency of factor VIIa (activated factor VII) is expressed in international units and preparations may be assayed using the first International Standard for blood coagulation factor VIIa concentrate (1993).

Adverse Effects and Precautions

Use of eptacog alfa (activated) may be associated with minor skin reactions, fever, headache, and changes in blood pressure. Eptacog alfa (activated) should be used with caution in patients with conditions associated with circulating tissue factor, such as advanced atherosclerosis, crush injury, or septicaemia, since there is a risk of precipitating thrombosis or disseminated intravascular coagulation.

Effects on the cardiovascular system. Reports of 185 serious thromboembolic events associated with eptacog alfa (activated), that had been received by the FDA up to the end of 2004, have been reviewed.[1] Data were collected from both clinical trials and spontaneous reports. Various forms of arterial and venous thrombosis had been described, and most events were found to have occurred after its use for unlicensed indications in patients without haemophilia.

1. O'Connell KA, *et al.* Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA* 2006; **295:** 293–8.

Uses and Administration

Factor VII may be used as replacement therapy in patients with rare genetic deficiencies of factor VII.

Factor VIIa (activated factor VII) is used to treat bleeding episodes and to prevent bleeding associated with surgery in patients with haemophilia A or haemophilia B who have developed antibodies to factor VIII or factor IX, respectively, and in acquired haemophilia (see Haemophilias, p.1048). It may also be used in congenital factor VII deficiency and Glanzmann's thrombasthenia (see Inherited Haemorrhagic Disorders, p.1050). Factor VIIa may also be useful in patients with von Willebrand's disease (p.1051). Factor VIIa is given as the recombinant form, eptacog alfa (activated). Eptacog alfa (activated) 100 micrograms is equivalent to 5000 international units.

In the treatment of bleeding episodes in patients with **haemophilia**, an initial dose of eptacog alfa (activated) 90 micrograms/kg is given by intravenous bolus injection over 2 to 5 minutes. Further doses may be given as required to achieve and maintain haemostasis, initially every 2 to 3 hours. The dose may then be adjusted (effective doses have ranged from 35 to 120 micrograms/kg), or the dosing interval increased, according to response. Treatment may need to be continued for up to 3 weeks or more following serious bleeding episodes. A similar regimen may be used in patients with haemophilia when they undergo an invasive procedure or surgery, in which case the initial dose should be given immediately before the intervention.

In **factor VII deficiency**, the usual dose of eptacog alfa (activated) for treating bleeding episodes due to surgery or invasive procedures is 15 to 30 micrograms/kg every 4 to 6 hours until haemostasis is achieved.

In **Glanzmann's thrombasthenia** that is refractory to platelet transfusions, the usual dose of eptacog alfa (activated) for treating bleeding episodes or preventing bleeding due to surgery or invasive procedures is 90 micrograms/kg every 2 hours; at least 3 doses should be given.

◊ Reviews.

1. Poon M-C. Use of recombinant factor VIIa in hereditary bleeding disorders. *Curr Opin Hematol* 2001; **8:** 312–18.
2. Midathada MV, *et al.* Recombinant factor VIIa in the treatment of bleeding. *Am J Clin Pathol* 2004; **121:** 124–37.
3. Anonymous. Novoseven for non-hemophilia hemostasis. *Med Lett Drugs Ther* 2004; **46:** 33–4.
4. Mathew P. The use of rFVIIa in non-haemophilia bleeding conditions in paediatrics: a systematic review. *Thromb Haemost* 2004; **92:** 738–46.
5. Parameswaran R, *et al.* Dose effect and efficacy of rFVIIa in the treatment of haemophilia patients with inhibitors: analysis from the Hemophilia and Thrombosis Research Society Registry. *Haemophilia* 2005; **11:** 100–106.
6. Siddiqui MAA, Scott LJ. Recombinant factor VIIa (eptacog alfa): a review of its use in congenital or acquired haemophilia and other congenital bleeding disorders. *Drugs* 2005; **65:** 1161–77.
7. Mariani G, *et al.* Congenital factor VII deficiency: therapy with recombinant activated factor VII—a critical appraisal. *Haemophilia* 2006; **12:** 19–27.

Administration. Recombinant factor VIIa is usually given by bolus intravenous injection. The successful use of continuous infusion has been described in a few small studies and case reports.[1]

1. Stachnik JM, Gabay MP. Continuous infusion of coagulation factor products. *Ann Pharmacother* 2002; **36:** 882–91.

Haemorrhagic disorders. As well as being used in patients with haemophilia, recombinant factor VIIa has been tried or investigated in patients with bleeding of various other causes.[1] There have been reports of recombinant factor VIIa used to manage or prevent bleeding in patients receiving warfarin[2-4] or a low-molecular-weight heparin.[5] There are also a few reports of it successfully controlling bleeding associated with diffuse alveolar haemorrhage[6-8] or dengue haemorrhagic fever;[9] it has also been studied in the management of acute variceal bleeding (p.2346). In the management of massive postpartum haemorrhage (p.2003), recombinant factor VIIa is increasingly being used when standard medical and surgical therapies are inadequate. There are suggestions that it may reduce the need for blood products, control bleeding sufficiently to allow transfer of the patient to a facility where angiography and embolisation can be performed, and reduce the need for hysterectomy.[10] However, evidence consists largely of case reports and case series. Although advice has been published, based on this evidence and expert opinion,[11] the place of recombinant factor VIIa in the treatment of postpartum haemorrhage remains to be confirmed. Initial investigation of recombinant factor VIIa in the acute management of intracerebral haemorrhage was promising,[12] but a phase 3 study found that it did not reduce the rates of death or severe disability, compared with placebo.[13] Recombinant factor VIIa is also under investigation in the management of serious bleeding after surgery or trauma.[14,15]

1. Lam MSH, Sims-McCallum RP. Recombinant factor VIIa in the treatment of non-hemophiliac bleeding. *Ann Pharmacother* 2005; **39:** 885–91.
2. Deveras RAE, Kessler CM. Reversal of warfarin-induced excessive anticoagulation with recombinant human factor VIIa concentrate. *Ann Intern Med* 2002; **137:** 884–8.

3. Freeman WD, *et al.* Recombinant factor VIIa for rapid reversal of warfarin anticoagulation in acute intracranial hemorrhage. *Mayo Clin Proc* 2004; **79:** 1495–1500.
4. Talkad A, *et al.* Reversal of warfarin-induced anticoagulation with factor VIIa prior to rt-PA in acute stroke. *Neurology* 2005; **64:** 1480–1.
5. Hu Q, Brady JO. Recombinant activated factor VII for treatment of enoxaparin-induced bleeding. *Mayo Clin Proc* 2004; **79:** 827.
6. Betensley AD, Yankaskas JR. Factor VIIa for alveolar hemorrhage in microscopic polyangiitis. *Am J Respir Crit Care Med* 2002; **166:** 1291–2.
7. Pastores SM, *et al.* Diffuse alveolar hemorrhage after allogeneic hematopoietic stem-cell transplantation: treatment with recombinant factor VIIa. *Chest* 2003; **124:** 2400–2403.
8. Henke D, *et al.* Successful treatment of diffuse alveolar hemorrhage with activated factor VII. *Ann Intern Med* 2004; **140:** 493–4.
9. Chuansumrit A, *et al.* The use of recombinant activated factor VII for controlling life-threatening bleeding in dengue shock syndrome. *Blood Coag Fibrinol* 2004; **15:** 335–42.
10. Karalapillai D, Popham P. Recombinant factor VIIa in massive postpartum haemorrhage. *Int J Obstet Anesth* 2007; **16:** 29–34.
11. Welsh A, *et al.* Guidelines for the use of recombinant activated factor VII in massive obstetric haemorrhage. *Aust N Z J Obstet Gynaecol* 2008; **48:** 12–16.
12. Mayer SA, *et al.* Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2005; **352:** 777–85.
13. Mayer SA, *et al.* FAST Trial Investigators. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2008; **358:** 2127–37.
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).