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.