that etamsylate produced about a 10 to 15% reduction in menstrual blood loss.[3] Etamsylate is now considered to be less effective than other treatments for menorrhagia, and is no longer recommended.[4]

1. Chamberlain G, *et al.* A comparative study of ethamsylate and mefenamic acid in dysfunctional uterine bleeding. *Br J Obstet Gynaecol* 1991; **98:** 707–11.
2. Bonnar J, Sheppard BL. Treatment of menorrhagia during menstruation: randomised controlled trial of ethamsylate, mefenamic acid, and tranexamic acid. *BMJ* 1996; **313:** 579–82.
3. Coulter A, *et al.* Treating menorrhagia in primary care: an overview of drug trials and a survey of prescribing practice. *Int J Technol Assess Health Care* 1995; **11:** 456–71.
4. National Collaborating Centre for Women's and Children's Health/NICE. Heavy menstrual bleeding (issued January 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/CG44FullGuideline.pdf (accessed 06/03/08)

Neonatal intraventricular haemorrhage. Etamsylate is one of several drugs that have been tried in the prevention of intraventricular haemorrhage in very low birth-weight infants (p.1050). In a multicentre, placebo-controlled, double-blind study,[1] etamsylate was given in an initial dose of 12.5 mg/kg intravenously or intramuscularly within 1 hour of delivery, followed by the same dose intravenously every 6 hours for 4 days to a total dose of 200 mg/kg. Of 330 infants who had had no evidence of haemorrhage soon after delivery, the subsequent incidence of haemorrhage in the 162 who received etamsylate was reduced, particularly the more extensive grades when compared with the 168 who received placebo. Of a further 30 infants with evidence of periventricular haemorrhage before treatment, 21 were given etamsylate and 9 placebo; treatment with etamsylate limited the extension of bleeding. There was also a reduction in patent ductus arteriosus in the treated infants. However, a subsequent study using the same dosage regimen,[2] showed little benefit on short-term follow-up. It was considered that the study size may have been too small and the drug given too late; the initial dose was given within 4 hours of birth whereas, in the previous study, treatment was started within 1 hour of birth. Follow-up[3] of these infants at 2 years of age found that etamsylate had not reduced the risk of death, impairment, or disability. Developmental outcome assessments at about 4 years of age in patients from the first study[4] also found that despite the original reduction in intraventricular haemorrhage with etamsylate, it had not reduced cerebral palsy compared with the control group.

1. Benson JWT, *et al.* Multicentre trial of ethamsylate for prevention of periventricular haemorrhage in very low birthweight infants. *Lancet* 1986; **ii:** 1297–1300.
2. The EC Ethamsylate Trial Group. The EC randomised controlled trial of prophylactic ethamsylate for very preterm neonates: early mortality and morbidity. *Arch Dis Child* 1994; **70:** F201–F205.
3. Elbourne D, *et al.* Randomised controlled trial of prophylactic etamsylate: follow up at 2 years of age. *Arch Dis Child Fetal Neonatal Ed* 2001; **84:** F183–F187.
4. Schulte J, *et al.* Developmental outcome of the use of etamsylate for prevention of periventricular haemorrhage in a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2005; **90:** F31–F35.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Impedil; ***Belg.:*** Dicynone; ***Braz.:*** Dicinone; ***Chile:*** Om-Dicynone†; ***Cz.:*** Dicynone; ***Fr.:*** Dicynone; ***Hung.:*** Dicynone; ***India:*** Alstat; Ethacid; Ethamcip; Ethasyl; Hemsyl; Revici-E; ***Indon.:*** Dicynone; ***Irl.:*** Dicynene; ***Ital.:*** Dicynone; Eselin; ***Mex.:*** Dicynone; ***Rus.:*** Dicynone (Дицинон); ***Singapore:*** Dicynone†; ***Spain:*** Dicinone; Hemo 141; ***Switz.:*** Dicynone; ***UK:*** Dicynene; ***Venez.:*** Dicynone.

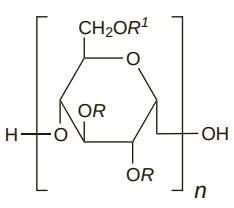
Etherified Starches ⊗

Almidón, éteres de; HES; Hydroxyethyl Starch; Hydroxyéthylamidon; Hydroxyethylamylum. 2-Hydroxyethyl ether starch.

CAS — 9005-27-0.

ATC — B05AA07.

ATC Vet — QB05AA07.



in which either *R* or R^1 may be either H or CH_2CH_2OH

(hetastarch)

Description. Etherified starches are starches that are composed of more than 90% of amylopectin and that have been etherified to varying extents.

- hetastarch (*BAN, USAN*): an average of 7 to 8 of the hydroxy groups in each 10 D-glucopyranose units of starch polymer have been converted into OCH_2CH_2OH groups
- pentastarch (*BAN, USAN*): an average of 4 to 5 of the hydroxy groups in each 10 D-glucopyranose units of the starch polymer have been converted to OCH_2CH_2OH groups

Etherified starches also vary in terms of average molecular weight and the position of etherification within the glucopyranose unit.

Incompatibility. Hetastarch is incompatible with many compounds including a number of injectable antibacterials.

References.

1. Wohlford JG, Fowler MD. Visual compatibility of hetastarch with injectable critical-care drugs. *Am J Hosp Pharm* 1989; **46:** 995–6.
2. Wohlford JG, *et al.* More information on the visual compatibility of hetastarch with injectable critical-care drugs. *Am J Hosp Pharm* 1990; **47:** 297–8.

Adverse Effects and Precautions

Hypersensitivity reactions including anaphylactic reactions have occurred after infusion of etherified starches. Pruritus can occur after long-term use of high doses of etherified starches; the onset may be delayed until weeks after the last infusion. Serum-amylase concentrations may appear to increase during infusion of etherified starches due to formation of an enzyme-substrate complex that is only eliminated slowly.

Precautions that should be observed with plasma expanders are described under Dextran 70, p.1060, and these should be considered when etherified starches are used. There may be some interference with blood grouping and cross-matching of blood.

◊ Reviews.

1. Wiedermann CJ. Hydroxyethyl starch - can the safety problems be ignored? *Wien Klin Wochenschr* 2004; **116:** 583–94.

Effects on the blood. Use of plasma expanders causes dilution of clotting factors and may also have direct effects on coagulation. Effects of etherified starches on the coagulation system include[1,2] a decrease in clotting factor VIII and von Willebrand factor that results in an acquired type I von Willebrand disease (see p.1051), a prolongation of the activated partial thromboplastin time, and a reduction in platelet volume. The extent of these effects appears to depend on the molecular weight and the rate of degradation *in vivo* of the starch. Etherified starches of high molecular weight that are more slowly degraded (due to a high degree of substitution or a high ratio of hydroxyethylation at the C2:C6 positions) have a greater effect on blood coagulation than medium and low molecular weight, easily degraded, etherified starches. Coagulopathy and haemorrhage have been reported with the use of solutions of etherified starches.[1,3] Serious complications such as intracranial bleeding and cerebral oedema have been reported in studies of patients with ischaemic stroke and other brain injuries who have been treated with etherified starches of various molecular weights and degrees of substitution, and several trials have been stopped prematurely as a result.[4]

1. Treib J, *et al.* Coagulation disorders caused by hydroxyethyl starch. *Thromb Haemost* 1997; **78:** 974–83.
2. de Jonge E, Levi M. Effects of different plasma substitutes on blood coagulation: a comparative review. *Crit Care Med* 2001; **29:** 1261–7.
3. Jonville-Béra A-P, *et al.* Acquired type I von Willebrand's disease associated with highly substituted hydroxyethyl starch. *N Engl J Med* 2001; **345:** 622–3.
4. Wiedermann CJ. Complications of hydroxyethyl starch in acute ischemic stroke and other brain injuries. *Pathophysiol Haemost Thromb* 2003; **33:** 225–8.

Effects on the kidneys. Osmotic-nephrosis-like lesions found at biopsy in some transplanted kidneys have been attributed to use of solutions of etherified starches in the donor patient.[1] Such use has also been reported to impair immediate graft function.[2] However, another study[3] found no association between the use of these solutions in the donor patient and osmotic-nephrosis-like lesions or delayed graft function. Oliguric acute renal failure and osmotic-nephrosis-like lesions occurred in a patient who was given an etherified starch infusion during surgery for carcinoma of the tonsils.[4]

Etherified starches should be used with caution in patients with renal impairment.[5]

1. Legendre CH, *et al.* Hydroxyethylstarch and osmotic-nephrosis-like lesions in kidney transplantation. *Lancet* 1993; **342:** 248–9.
2. Cittanova ML, *et al.* Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients. *Lancet* 1996; **348:** 1620–22.
3. Coronel B, *et al.* Hydroxyethylstarch and renal function in kidney transplant recipients. *Lancet* 1997; **349:** 884.
4. De Labarthe A, *et al.* Acute renal failure secondary to hydroxyethylstarch administration in a surgical patient. *Am J Med* 2001; **111:** 417–18.
5. Boldt J. Hydroxyethylstarch as a risk factor for acute renal failure: is a change of clinical practice indicated? *Drug Safety* 2002; **25:** 837–46.

Effects on the skin. Pruritus has been reported after infusion of etherified starches.[1] It appears to be associated with tissue deposition of the starch although the actual mechanism by which this provokes pruritus is unresolved. The effect appears to be dose-related, which may explain the differences in reported incidences that have ranged from less than 10% to more than 60% of patients being affected. The molecular weight and degree of substitution of the etherified starch do not appear to be risk factors. The pruritus is usually generalised, but there are reports of localised pruritus affecting the trunk, extremities, anogenital area, and head and neck. It is frequently severe, persistent, and refractory to treatment, causing sleep disturbances and adversely affecting quality of life. Attacks of pruritus may be precipitated by heat, sweating, exercise, bathing, mechanical pressure, and mental stress. It typically has a delayed onset of 1 to 6 weeks after exposure to the etherified starch. Average durations of 9 to 15 weeks have been reported, but in some cases pruritus has continued for up to 2 years. The condition is generally unresponsive to treatment, although there have been reports of relief with topical capsaicin, ultraviolet therapy, or oral naltrexone.

Marked and persistent periocular swelling developed in a patient after 15 daily infusions of hetastarch.[2] Abnormal accumulation of hetastarch was found in the periocular tissues.

1. Bork K. Pruritus precipitated by hydroxyethyl starch: a review. *Br J Dermatol* 2005; **152:** 3–12.
2. Kiehl P, *et al.* Decreased activity of acid α-glucosidase in a patient with persistent periocular swelling after infusions of hydroxyethyl starch. *Br J Dermatol* 1998; **138:** 672–77.

Pharmacokinetics

Etherified starches consist of mixtures of molecules with a range of molecular weights and with varying degrees of etherification. After intravenous infusion the molecules with a molecular weight of less than 50 000 are readily excreted unchanged by the kidney; larger molecules are metabolised and eliminated more slowly. The rate of metabolism depends upon the size of the molecule and the degree and position of etherification, with a high molecular weight, high degree of etherification, and etherification predominantly at the C2 position leading to a slower rate of metabolism and hence a longer duration of action. About 33% of a dose of high-molecular-weight hetastarch (weight average molecular weight 450 000) and about 70% of a dose of medium-molecular-weight pentastarch (weight average molecular weight 250 000) is excreted in the urine in 24 hours. Etherified starches may be distributed to various tissues; a small proportion of the dose may persist in the body for several years.

◊ References.

1. Mishler JM, *et al.* Changes in the molecular composition of circulating hydroxyethyl starch following consecutive daily infusions in man. *Br J Clin Pharmacol* 1979; **7:** 505–9.
2. Mishler JM, *et al.* Post-transfusion survival of hydroxyethyl starch 450/0.70 in man: a long-term study. *J Clin Pathol* 1980; **33:** 155–9.
3. Yacobi A, *et al.* Pharmacokinetics of hydroxyethyl starch in normal subjects. *J Clin Pharmacol* 1982; **22:** 206–12.
4. Jungheinrich C, Neff TA. Pharmacokinetics of hydroxyethyl starch. *Clin Pharmacokinet* 2005; **44:** 681–99.

Uses and Administration

Etherified starches are plasma volume expanders used in the management of hypovolaemic shock (p.1183). Those most commonly used include high-molecular-weight hetastarch (weight average molecular weight 450 000 to 480 000) and medium-molecular-weight pentastarch (weight average molecular weight 200 000 to 250 000). Other etherified starches that are used include low-molecular-weight pentastarch and medium-molecular-weight hexastarch, which has a degree of etherification between that of pentastarch and hetastarch. A higher molecular weight hetastarch is also available. Iso-oncotic solutions of etherified starches, for example, 6% hetastarch or 6% medium-molecular-weight pentastarch, exert a similar colloidal osmotic pressure to human albumin, and when given by intravenous infusion produce an expansion of plasma volume slightly in excess of the infused volume. Hyperoncotic solutions, for example 10% medium-molecular-weight pentastarch, produce an expansion of plasma volume of about 1.5 times the infused volume. The du-

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.