lar coagulation. The risk should be less with more highly purified preparations.

As with other plasma derivatives there is a possibility of transmitting viral infection, although selection of donors and heat or chemical treatments of products are used to minimise the risk. Vaccination against hepatitis A and B is recommended for patients not already immune.

Antibodies to factor IX may develop rarely.

Effects on the cardiovascular system. Some factor IX preparations derived from plasma contain other clotting factors in addition to factor IX (prothrombin complex concentrates), and some preparations have also contained activated clotting factors. Such preparations have the potential to produce thromboembolic complications.[1,2] Reported complications include arterial and venous thrombosis, pulmonary embolism, acute myocardial infarction, and disseminated intravascular coagulation. Risk factors in haemophiliacs include liver disease, severe muscle haemorrhages, crush injuries, immobilisation, and orthopaedic surgery. Rapid infusion of factor IX concentrates, or repeated large doses, may also increase the risk of thromboembolism. The risks of thromboembolism have been reduced with the development of more purified prothrombin complex concentrates, and highly purified factor IX preparations that do not contain other clotting factors.[1,3]

1. Köhler M. Thrombogenicity of prothrombin complex concentrates. *Thromb Res* 1999; **95** (suppl): S13–S17.
2. Najaf SM, *et al.* Myocardial infarction during factor IX infusion in hemophilia B: case report and review of the literature. *Ann Hematol* 2004; **83:** 604–7.
3. Santagostino E, *et al.* Markers of hypercoagulability in patients with hemophilia B given repeated, large doses of factor IX concentrates during and after surgery. *Thromb Haemost* 1994; **71:** 737–40.

Uses and Administration

Factor IX is used as replacement therapy in patients with haemophilia B (Christmas disease), a genetic deficiency of factor IX (see Haemophilias, p.1048).

There are two forms of factor IX preparation derived from plasma; one is of high purity, the other is rich in other clotting factors (prothrombin complex concentrates). A recombinant factor IX preparation, nonacog alfa, is also available. Preparations that contain other factors as well as factor IX may sometimes be useful for the treatment of bleeding due to deficiencies of factors II, VII, and X, as well as IX, and in the preparation of such patients for surgery; they may also be used for immediate reversal of coumarin anticoagulants and in the management of patients with haemophilia A who have antibodies to factor VIII.

Factor IX is given by slow intravenous infusion. In patients with factor IX deficiency the dosage should be determined for each patient and will vary with the preparation used and the circumstances of bleeding or type of surgery to be performed. Suggested target factor IX concentrations for patients with haemophilia B vary, but the following have been suggested:

- for mild to moderate haemorrhage the plasma concentration of factor IX should be raised to 20 to 30% of normal
- for more serious haemorrhage or minor surgery it should be raised to 30 to 60% of normal
- for severe haemorrhage or major surgery an increase to 60 to 100% of normal may be necessary

Calculation of the appropriate dose varies according to the manufacturers' recommendations.

For long-term prophylaxis in severe haemophilia B, doses of 20 to 40 international units/kg every 3 or 4 days, as required, may be used.

Preparations

Ph. Eur.: Human Coagulation Factor IX; Human Prothrombin Complex; ***USP 31:*** Factor IX Complex.

Proprietary Preparations (details are given in Part 3)
Arg.: Aimafix; Benefix; Berinin P; Immunine; Mononine; Octanine; Protromplex; Replenine†; ***Austral.:*** Benefix; Monofix-VF; ***Austria:*** Benefix; Beriplex; Immunine; Octanine; Octaplex; Prothromplex S-TIM 4; ***Belg.:*** Benefix; Mononine; Octanine; PPSB Conc SD; ***Braz.:*** Bebulin†; Benefix†; Berinin; Beriplex PN; Immunine†; Mononine; Octanyne†; Prothrompelx-T†; Replenine†; ***Canad.:*** Benefix; Immunine; Mononine; ***Chile:*** Aimafix; Benefix†; Octanyne†; ***Cz.:*** Benefix; Immunine; Mononine; Nonafact; Octanine; Prothromplex; ***Denm.:*** Benefix; Immunine†; Mononine†; ***Fin.:*** Bemofil†; Benefix; Nonafact; ***Fr.:*** Benefix; Betafact; Kaskadil; Mononine; Octafix; ***Ger.:*** Alphanine; Benefix; Berinin; Beriplex PN; Immunine; Mononine; Octanine; Octaplex; PPSB Konzentrat S-TIM; Prothrombinkomplex BaWu†; ***Gr.:*** Benefix; Betafact; Mononine; Replenine; ***Hong Kong:*** Alphanine; Profilnine; Proplex T†; ***Hung.:*** Berinin P; Beriplex PN; Humafactor-9; Immunine; Octanine F; Prothromplex; ***Irl.:*** Mononine†; ***Israel:*** Betafact; Profilnine; Proplex; Replenine; ***Ital.:*** Aimafix; Alphanine; Benefix; Immunine; Mononine; Protromplex TIM 3; Uman-Complex DI; ***Malaysia:*** Alphanine; Profilnine; Proplex T†; Replenine; ***Mex.:*** Benefix†; Berinin P; Immunine†; Konyne†; Octanine F; Replenine; ***Neth.:*** Alphanine; Benefix; Betafact; Immunonine; Mononine; Nonafact; ***Norw.:*** Benefix; ***NZ:*** Benefix; Monofix; Prothrombinex; ***Philipp.:*** Alphanine; Profilnine; ***Pol.:*** Immunine; Prothromplex; ***Port.:*** Benefix; Betafact; Immunine; Mononine; Nanotiv; Nonafact; Octaninef; Octaplex; ***Rus.:*** Aimafix (Аимафикс); Octanine (Октанайн Ф); ***S.Afr.:*** Haemosolvex; Prothromplex-T TIM 4; ***Singapore:*** Alphanine; Profilnine; Replenine; ***Spain:*** Benefix; Berinin P; Immunine; Mononine; Nanotiv; Prothrompelx; ***Swed.:*** Benefix; Immunine; Mononine; Nanotiv; ***Switz.:*** Benefix; Berinin HS; Beriplex; Immunine; Octanine F; Prothromplex Total S-TIM 4; ***Thai.:*** Alphanine; Octanine; Profilnine; ***Turk.:*** Aimafix; Berinin P; Betafact; Immunine; Kaskadil; Konyne; Octanine F; Octanyne; Replenine; ***UK:*** Alphanine; Benefix; Beriplex PN; Defix†; Hipfix†; Mononine; Replenine; ***USA:*** Alphanine; Bebulin VH; Benefix; Mononine; Profilnine; Proplex T; ***Venez.:*** Immunine†; Proplex†.

Multi-ingredient: ***Arg.:*** Beriplex PN.

Factor XI

Facteur XI; Plasma Thromboplastin Antecedent; PTA.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Human Coagulation Factor XI; Factor XI Coagulationis Humanus; Dried Factor XI Fraction BP 2008). A plasma protein fraction that contains coagulation factor XI. 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 XI fraction is dissolved in a suitable liquid, distributed aseptically into the final containers, and immediately frozen. The preparation is freeze-dried and the containers sealed under vacuum or under nitrogen. Heparin, C_1-esterase inhibitor, and antithrombin III, may be added. No antimicrobial preservative is added. When reconstituted as stated on the label the resulting solution contains not less than 50 units/mL.
A white or almost white powder or friable solid. pH of the reconstituted preparation is 6.8 to 7.4. Store at a temperature of 2° to 8°. Protect from light.

Profile

Factor XI is used as replacement therapy in patients with congenital factor XI deficiency (haemophilia C; see Inherited Haemorrhagic Disorders, p.1050) for the prevention and treatment of haemorrhage. The dose is based on the degree of factor XI deficiency and the condition of the patient.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Hemoleven.

Factor XIII

Fibrin-stabilising Factor; FSF.
ATC — B02BD07.
ATC Vet — QB02BD07.

Profile

Factor XIII is used as replacement therapy in patients with a genetic deficiency of factor XIII (see Inherited Haemorrhagic Disorders, p.1050). It may also be used in patients with acquired deficiency of factor XIII (see Acquired Haemorrhagic Disorders, p.1047), and for supportive therapy in postoperative wound healing. Dosage of factor XIII is based on the degree of deficiency and the condition of the patient. For prophylaxis of haemorrhage in patients with genetic deficiency about 10 units/kg may be given intravenously once a month. The interval between doses may be shortened if spontaneous haemorrhage occurs. For pre-operative use, a dose of up to 35 units/kg may be given immediately before the operation and followed by adequate doses to maintain efficacy until the wound is healed. For the treatment of severe bleeding episodes 10 to 20 units/kg should be given daily, until bleeding stops. In acute bleeding, especially intracranial bleeding, doses of up to 50 units/kg may be needed to raise factor XIII to normal levels. Doses of at least 15 to 20 units/kg may be required for the treatment of haemorrhage in acquired factor XIII deficiency. In the promotion of postoperative wound healing, a dose of 10 units/kg may be given on the day of the operation and on each of the next 3 days. Like other clotting factor preparations (see Factor VIII, p.1067), the use of factor XIII may be associated with risks of hypersensitivity reactions, thrombosis, and viral infection transmission; inhibitors of factor XIII may occur very rarely.

Cryoprecipitate is also used as a source of factor XIII.

Factor XIII is also a component of fibrin glues (see Fibrin, p.1069).

Inflammatory bowel disease. Some patients with inflammatory bowel disease (p.1697) may be deficient in factor XIII, possibly due to increased intestinal blood loss seen in severe ulcerative colitis or increased mucosal deposition of factor XIII in Crohn's disease. Factor XIII concentrate given intravenously has produced beneficial results in 12 patients with active ulcerative colitis resistant to conventional therapy with corticosteroids and mesalazine[1] and has also been associated with healing of intractable fistulae in 3 of 4 patients with Crohn's disease.[2] However, a controlled study[3] found no benefit from factor XIII in active corticosteroid-refractory ulcerative colitis.

1. Lorenz R, *et al.* Factor XIII substitution in ulcerative colitis. *Lancet* 1995; **345:** 449–50.
2. Oshitani N, *et al.* Treatment of Crohn's disease fistulas with coagulation factor XIII. *Lancet* 1996: **347:** 119–20.
3. Bregenzer N, *et al.* Lack of clinical efficacy of additional factor XIII treatment in patients with steroid refractory colitis. *Z Gastroenterol* 1999; **37:** 999–1004.

Wounds and ulcers. Topical factor XIII has been reported to promote wound healing in patients with refractory leg ulcers.[1-3]

1. Wozniak G, *et al.* Factor XIII in ulcerative leg disease: background and preliminary clinical results. *Semin Thromb Hemost* 1996; **22:** 445–50.
2. Herouy Y, *et al.* Factor XIII-mediated inhibition of fibrinolysis and venous leg ulcers. *Lancet* 2000; **355:** 1970–1.
3. Hildenbrand T, *et al.* Treatment of nonhealing leg ulcers with fibrin-stabilizing factor XIII: a case report. *Dermatol Surg* 2002; **28:** 1098–9.

Preparations

Ph. Eur.: Fibrin Sealant Kit.

Proprietary Preparations (details are given in Part 3)
Arg.: Fibrogammin P; ***Austria:*** Fibrogammin; ***Belg.:*** Fibrogammin; ***Braz.:*** Fibrogammin; ***Cz.:*** Fibrogammin P†; ***Ger.:*** Fibrogammin; ***Hong Kong:*** Fibrogammin P; ***Israel:*** Fibrogammin P; ***Switz.:*** Fibrogammin; ***UK:*** Fibrogammin P.

Multi-ingredient: ***Arg.:*** Beriplast P; Tissucol; Tissucol Duo Quick†; ***Austral.:*** Tisseel Duo; ***Austria:*** Beriplast; Tissucol; Tissucol Duo Quick; ***Belg.:*** Tissucol Duo; ***Braz.:*** Beriplast P; ***Canad.:*** Tisseel; ***Chile:*** Beriplast P; ***Cz.:*** Tissucol; ***Denm.:*** Tisseel Duo Quick; ***Fin.:*** Tisseel Duo Quick; ***Fr.:*** Beriplast; Tissucol; ***Ger.:*** Beriplast; Tissucol Duo S; Tissucol-Kit; ***Gr.:*** Beriplast P; ***Hong Kong:*** Beriplast P; Tisseel; ***Hung.:*** Beriplast P; Tissucol-Kit; ***Indon.:*** Beriplast; ***Israel:*** Beriplast; Tisseel; ***Ital.:*** Beriplast; ***Mex.:*** Beriplast P; Tissucol†; ***Neth.:*** Beriplast P; Tissucol; Tissucol Duo; ***Pol.:*** Beriplast; ***Port.:*** Tissucol Duo; ***Spain:*** Beriplast P Combi; Tissucol Duo; ***Swed.:*** Tisseel Duo Quick; ***Switz.:*** Beriplast P; Tissucol; Tissucol Duo S; ***Turk.:*** Beriplast P; ***UK:*** Tisseel.

Fibrin *(rINN)*

Fibrina; Fibrine; Fibrinum.

Фибрин

Pharmacopoeias. Many pharmacopoeias have monographs for fibrin preparations, including *Eur.* (see p.vii).
Ph. Eur. 6.2 (Fibrin Sealant Kit; Fibrini Glutinum). It is composed of two components, a fibrinogen concentrate containing human fibrinogen (component 1), and a human thrombin preparation (component 2). The kit may also contain other ingredients, such as human factor XIII, a fibrinolysis inhibitor, or calcium ions. Stabilisers such as human albumin may be added. The human constituents are obtained from plasma for fractionation and the method of preparation includes a step or steps that have been shown to remove or inactivate known agents of infection. The constituents are passed through a bacteria-retentive filter and distributed aseptically into sterile containers. Containers of freeze-dried constituents are sealed under vacuum or filled with oxygen-free nitrogen or other suitable inert gas before sealing. No antimicrobial preservative is added. When thawed or reconstituted as stated on the label, the fibrinogen concentrate contains not less than 40 g/litre of clottable protein; the activity of the thrombin preparation varies over a wide range (about 4 to 1000 international units/mL). Protect from light.

Profile

Fibrin glue is prepared by mixing solutions containing fibrinogen, thrombin, and calcium ions, with the addition of aprotinin to inhibit fibrinolysis. It may also include factor XIII and other clotting components. Fibrin glue is used as a haemostatic to control haemorrhage during surgical procedures or as a spray to bleeding surfaces.

A dry artificial sponge of human fibrin, known as human fibrin foam, has been used similarly; it is prepared by clotting human thrombin with a foam of human fibrinogen solution. A collagen sponge coated with thrombin and fibrinogen is also available.

Adverse effects. Fatal neurotoxicity has been reported[1] after the use of a fibrin sealant during neurosurgical procedures. The toxicity may have been due to the presence of tranexamic acid as a stabiliser in the formulation, and such formulations should not be used in surgical operations where contact with the CSF or dura mater could occur.[2]

For rare reports of hypersensitivity reactions to aprotinin used locally as a component of fibrin sealant, see p.1055.

1. Committee on Safety of Medicines/Medicines Control Agency. Quixil human surgical sealant: reports of fatal reactions. *Current Problems* 1999; **25:** 19. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023713&RevisionSelectionMethod=LatestReleased (accessed 31/05/06)
2. Committee on Safety of Medicines/Medicines Control Agency. Quixil human surgical sealant: update on fatal neurotoxic reactions. *Current Problems* 2000; **26:** 10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007460&RevisionSelectionMethod=LatestReleased (accessed 31/05/06)

Use. Reviews.

1. Dunn CJ, Goa KL. Fibrin sealant: a review of its use in surgery and endoscopy. *Drugs* 1999; **58:** 863–86.