Preparations of factor VIII may be derived from human plasma or recombinant sources. They are used to control bleeding episodes in the treatment of patients with haemophilia A and to prevent bleeding episodes in such patients undergoing dental and surgical procedures. They may also be used for long-term prophylaxis in patients with severe haemophilia A.

Preparations of factor VIII are given by slow intravenous injection or short infusion, and some octocog alfa preparations may also be given by continuous infusion. The dosage of factor VIII should be determined for each patient and will vary with the circumstances involving bleeding or type of surgery to be performed. In adults, a dose of 1 international unit/kg has been reported to raise the plasma concentration of factor VIII by about 2% (of normal). The response may be lower in children. A suggested formula to calculate, approximately, the dose required for a given effect is:

$$\text{units} = \text{wt (kg)} \times 0.5 \times \% \text{ desired increase (of normal)}$$

Recommended doses vary depending on the preparation used, but the following increments in plasma concentration of factor VIII have been suggested:

- for mild to moderate haemorrhage an increase to 20 to 30% of normal, usually with a single dose of 10 to 15 units/kg
- for more serious haemorrhage or minor surgery an increase to 30 to 50% of normal, by a usual initial dose of 15 to 25 units/kg followed by 10 to 15 units/kg every 8 to 12 hours if required
- for severe haemorrhage or major surgery an increase to 80 to 100% of normal may be necessary, the usual initial dose being 40 to 50 units/kg followed by 20 to 25 units/kg every 8 to 12 hours. Some octocog alfa preparations may also be given for major surgery as an initial pre-operative bolus followed by a continuous infusion, adjusted postoperatively to daily clearance and desired factor VIII concentrations

For long-term prophylaxis in severe haemophilia A, doses of 10 to 50 units/kg every 2 or 3 days, as required, may be used.

In patients with inhibitory antibodies to human factor VIII, a porcine factor VIII preparation may be used in doses of 25 to 150 units/kg depending upon the severity of the haemorrhage.

Some factor VIII concentrates also contain von Willebrand factor and these preparations may be used in the management of von Willebrand's disease (p.1051). Commercial very highly purified and recombinant factor VIII preparations do not contain appreciable amounts of von Willebrand factor and are thus ineffective.

Cryoprecipitate is an alternative source of clotting factors and contains factor VIII, factor XIII, von Willebrand factor, fibrinogen, and fibronectin. It has been used in the treatment of haemophilia A and von Willebrand's disease but safer more specific clotting factor alternatives are now available and preferred.

◊ Reviews.

1. McCormack PL, Plosker GL. Octocog alfa, plasma/albumin-free method. *Drugs* 2005; **65:** 2613–20.
2. Frampton JE, Wagstaff AJ. Sucrose-formulated octocog alfa: a review of its use in patients with haemophilia A. *Drugs* 2008; **68:** 839–53.

Administration. Surgical prophylaxis or significant haemorrhage in patients with haemophilia A is usually managed with injections of factor VIII given intravenously every 8 to 12 hours. However, continuous intravenous infusion has been used as an alternative.[1,2] It prevents wide fluctuations in factor VIII plasma concentrations and there is a progressive decrease in clearance associated with steady state. Studies have suggested that continuous infusion is as effective as bolus injection, but with a lower concentrate requirement. Concerns about continuous infusion include factor VIII stability, bacterial contamination, local irritation and thrombophlebitis, and inhibitor formation.

1. Stachnik JM, Gabay MP. Continuous infusion of coagulation factor products. *Ann Pharmacother* 2002; **36:** 882–91.
2. Schulman S. Continuous infusion. *Haemophilia* 2003; **9:** 368–75.

Preparations

Ph. Eur.: Human Coagulation Factor VIII; Human Coagulation Factor VIII (rDNA);
USP 31: Antihemophilic Factor; Cryoprecipitated Antihemophilic Factor.

Proprietary Preparations (details are given in Part 3)
Arg.: Beriate P; Emoclot; Fanhdi; Haemate; Haemoctin SDH; Hemofil M; Immunate; Koate-DVI†; Monarc-M†; Monoclate-P; Octanate; Recombinate; ReFacto†; ***Austral.:*** AHF†; Biostate; Kogenate; Recombinate; ReFacto; ***Austria:*** Advate; Beriate; Haemate; Haemoctin SDH; Helixate; Immunate; Kogenate; Monoclate-P†; Octanate; Recombinate; ReFacto; ***Belg.:*** Advate; Factane; Haemate; Helixate; Kogenate; Recombinate; ReFacto; ***Braz.:*** Beriate P; Fatori 8Y†; Haemate; Immunate†; Koate†; Kryobulin†; Monoclate-P; Octavi†; Vueffe†; ***Canad.:*** Helixate; Humate-P; Kogenate; Recombinate; ReFacto; ***Chile:*** Emoclot; Fanhdi; Koate-DVI; Octanate†; ***Cz.:*** Advate; Emoclot†; Fanhdi; Haemate; Haemoctin SDH; Helixate; Hemofil M†; Immunate; Kogenate; Metoda M†; Monoclate-P†; Octanate; Recombinate; ReFacto; ***Denm.:*** Advate; Haemate; Helixate; Kogenate; Monoclate-P†; Recombinate; ReFacto; ***Fin.:*** Advate; Amofil; Kogenate; Recombinate; ReFacto; ***Fr.:*** Advate; Factane; Helixate; Hemofil M†; Kogenate; Monoclate-P†; Recombinate; ReFacto; ***Ger.:*** Advate; Beriate P; Fanhdi; Haemate; Haemoctin SDH; Helixate; Hemofil†; Immunate; Kogenate; Monoclate-P†; Octanate; Profilate†; Recombinate; ReFacto; Wilate; ***Gr.:*** 8Y; Advate; Fanhdi; Fibrogammin P; Haemoctin; Helixate; Hemofil M; Immunate; Kogenate; Monoclate-P†; Octanate; Recombinate; ReFacto; ***Hong Kong:*** Alphanate; Haemate; Hemofil M; Koate-DVI; Recombinate; ***Hung.:*** Beriate P; Fanhdi; Haemate; Haemoctin SDH; Hemofil M; Humafactor-8; Immunate; Koate†; Kogenate; Octanate; Recombinate; ReFacto; ***Indon.:*** Koate; ***Irl.:*** Haemate†; Kogenate; Monoclate-P†; ReFacto; ***Israel:*** Fanhdi; Haemate; Haemoctin SDH; Hemofil M; Hyate:C; Koate; Monarc-M; Monoclate-P; Omrixate; Profilate; Recombinate; ***Ital.:*** Advate; Alphanate; Beriate P; Emoclot; Fanhdi; Haemate; Helixate; Hemofil M; Immunate; Kogenate; Recombinate; ReFacto; Uman-Cry DI†; Vueffe†; ***Jpn:*** Advate; Recombinate; ***Malaysia:*** Alphanate; Fanhdi; Hemofil; Koate-DVI†; ***Mex.:*** Emoclot†; Hemofil M†; Immunate†; Koate-DVI†; Monoclate-P; Octanate; ***Neth.:*** Advate; Alphanate; Haemate; Helixate; Hemofil; Immunate; Kogenate; Recombinate; ReFacto; ***Norw.:*** Helixate; Kogenate; Recombinate; ReFacto; ***NZ:*** Advate; AHF; Biostate; Kogenate; Octanate; Recombinate; ReFacto; ***Philipp.:*** Alphanate; Hemofil M; Koate-DVI; ***Pol.:*** Czynnik VIII (Metoda M); Haemoctin; Hemofil; Immunate; ***Port.:*** Beriate P; Emoclot; Factane; Fanhdi; Haemate; Haemoctin SDH; Helixate; Immunate; Kogenate; Octanate; Recombinate; ReFacto; Wilate; ***Rus.:*** Emoclot (Эмоклот); Koate (Коэйт-ДВИ); Octanate (Октанат); ***S.Afr.:*** Haemosolvate; ***Singapore:*** Alphanate; Fanhdi; Haemoctin SDH; Hemofil M†; Koate-DVI†; Optivate; ***Spain:*** Advate; Beriate P; Fanhdi; Haemate; Helixate; Hemofil M; Kogenate; Monoclate-P†; Octanate; Recombinate; ReFacto; ***Swed.:*** Advate; Beriate P†; Haemate; Helixate; Hemofil M†; Immunate; Kogenate; Monoclate-P†; Octonativ-M; Recombinate; ReFacto; ***Switz.:*** Advate; Beriate P; Haemate; Helixate; Immunate; Kogenate; Octanate; Recombinate; ReFacto; ***Thai.:*** Alphanate; Fanhdi; Haemoctin SDH; Hemoraas; Method M†; Octanate; ***Turk.:*** Beriate P; Emoclot; Factane; Fanhdi; Haemate; Haemoctin SDH; Haemoetin; Hemofil M; Immunate; Koate-DVI; Liberate; Monarc-M; Octanate; ***UK:*** Advate; Alphanate; Beriate P; Fanhdi; Haemate; Helixate; Hemofil M†; Hyate:C; Kogenate; Liberate†; Monoclate-P; Optivate; Recombinate; ReFacto; Replenate; ***USA:*** Advate; Alphanate; Bioclate†; Helixate; Hemofil M; Humate-P; Hyate:C†; Koate-DVI; Kogenate; Monarc-M; Monoclate-P; Recombinate; ReFacto; Xyntha; ***Venez.:*** Fandhi; Hemofil M†; Immunate†.

Multi-ingredient: ***Fr.:*** Innobranduo†.

Factor VIII Inhibitor Bypassing Fraction

Activated Prothrombin Complex Concentrate; Anti-inhibitor Coagulant Complex; Complejo coagulante antiinhibidor del factor VIII; Faktör VIII Inhibitör Baypaslayan Fraksiyonu.

ATC — B02BD03.
ATC Vet — QB02BD03.

Adverse Effects and Precautions

Hypersensitivity reactions may follow the use of preparations with factor VIII inhibitor bypassing activity. Rapid infusion may cause headache, flushing, and changes in blood pressure and pulse rate.

It should not be given if disseminated intravascular coagulation is suspected or if there are signs of fibrinolysis. It should be used with caution in patients with liver disease. The risk of thromboembolism may be increased with the use of high doses or in patients with thrombotic risk factors.

As with other plasma-derived products, there is a risk of transmission of infection.

Safety. References.

1. Ehrlich HJ, *et al.* Safety of factor VIII inhibitor bypass activity (FEIBA): 10-year compilation of thrombotic adverse events. *Haemophilia* 2002; **8:** 83–90.
2. Luu H, Ewenstein B. FEIBA safety profile in multiple modes of clinical and home-therapy application. *Haemophilia* 2004; **10** (suppl): 10–16.

Uses and Administration

Preparations with factor VIII inhibitor bypassing activity are prepared from human plasma and contain factors II, IX, and X, and activated factor VII; small amounts of factor VIII and factors of the kallikrein-kinin system are also present. They are used in patients with haemophilia A who have antibodies to factor VIII and in patients with acquired antibodies to factor VIII (see Haemophilias, p.1048). The dose is given intravenously and depends on the preparation used.

◊ References.

1. White GC. Seventeen years' experience with Autoplex/Autoplex T: evaluation of inpatients with severe haemophilia A and factor VIII inhibitors at a major haemophilia centre. *Haemophilia* 2000; **6:** 508–12.
2. Wilde JT. Evidence for the use of activated prothrombin complex concentrates (aPCCs) in the treatment of patients with haemophilia and inhibitors. *Pathophysiol Haemost Thromb* 2002; **32** (suppl): 9–12.
3. Sallah S. Treatment of acquired haemophilia with factor eight inhibitor bypassing activity. *Haemophilia* 2004; **10:** 169–73.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Feiba; ***Austria:*** Feiba; ***Belg.:*** Feiba; ***Braz.:*** Feiba†; ***Canad.:*** Feiba; ***Cz.:*** Feiba; Ocplex; ***Denm.:*** Feiba; ***Fin.:*** Feiba; ***Fr.:*** Feiba; ***Ger.:*** Autoplex†; Feiba; ***Hong Kong:*** Feiba†; ***Hung.:*** Feiba; ***Israel:*** Feiba; ***Ital.:*** Feiba; ***Malaysia:*** Autoplex T†; Feiba; ***Mex.:*** Feiba†; ***Neth.:*** Cofact; Feiba; ***NZ:*** Feiba; ***Pol.:*** Feiba; ***Port.:*** Feiba; ***S.Afr.:*** Feiba; ***Spain:*** Feiba; ***Swed.:*** Autoplex†; Feiba; Ocplex; ***Switz.:*** Feiba; ***Turk.:*** Feiba; ***UK:*** Feiba; ***USA:*** Autoplex T†; Feiba.

Factor IX

Christmas Factor; Facteur IX; Plasma Thromboplastin Component; PTC.

ATC — B02BD04.
ATC Vet — QB02BD04.

Description. Factor IX is a plasma protein involved in blood coagulation. It may be obtained from human plasma or produced by recombinant DNA technology. The name Nonacog Alfa is in use for recombinant factor IX.

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

Ph. Eur. 6.2 (Human Coagulation Factor IX; Factor IX Coagulationis Humanus; Dried Factor IX Fraction BP 2008). A plasma protein fraction containing coagulation factor IX, prepared by a method that effectively separates it from other prothrombin complex factors (factors II, VII, and X). It is prepared from human plasma obtained 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 maintain functional integrity of factor IX, 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 IX 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 are sealed under vacuum or under an inert gas. Heparin, antithrombin, or other auxiliary substances such as a stabiliser may be included. No antimicrobial preservative is added. The specific activity is not less than 50 international units of factor IX per mg of total protein before the addition of any protein stabiliser. The dried product is a white or pale yellow hygroscopic powder or friable solid. Store in airtight containers. Protect from light. When reconstituted as stated on the label the resulting solution contains not less than 20 international units/mL.

Ph. Eur. 6.2 (Human Prothrombin Complex; Prothrombinum Multiplex Humanum; Dried Prothrombin Complex BP 2008). It contains factor IX with variable amounts of coagulation factors II, VII, and X. It is prepared by fractionation of 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 in particular to minimise thrombogenicity and includes a step or steps that have been shown to remove or inactivate known agents of infection. The prothrombin complex fraction is dissolved in a suitable liquid, sterilised by filtration, distributed aseptically into final containers, and immediately frozen. The preparation is freeze-dried and the containers are sealed under vacuum or under an inert gas. No antimicrobial preservative is added. Heparin, antithrombin, and other auxiliary substances such as a stabiliser may be added. The potency of the preparation is not less than 0.6 international units of factor IX per mg of total protein before the addition of any protein stabiliser. The dried product is a white or slightly coloured, very hygroscopic, powder or friable solid. Store in airtight containers. Protect from light. When reconstituted as stated on the label the resulting solution contains not less than 20 international units/mL.

USP 31 (Factor IX Complex). A sterile freeze-dried powder consisting of partially purified factor IX fraction, as well as concentrated factor II, VII, and X fractions of venous plasma obtained from healthy human donors. It contains no preservatives. It should be stored at 2° to 8° in hermetically-sealed containers. It should be used within 4 hours after reconstitution and administered with equipment that includes a filter.

Nonacog Alfa *(BAN, USAN, rINN)*

Nonacogum Alfa; Nonakog Alfa; Nonakogialfa. Blood-coagulation factor IX (human), glycoform α; Blood-coagulation factor IX (synthetic human); .

Нонаког Альфа

CAS — 113478-33-4; 181054-95-5;.
ATC — B02BD09.
ATC Vet — QB02BD09.

Units

The activity of factor IX is expressed in terms of international units and preparations may be assayed using the third International Standard for blood coagulation factor IX concentrate, human (1996).

Adverse Effects and Precautions

Hypersensitivity reactions may follow the use of factor IX preparations and there may be chills and urticaria. Other adverse effects include nausea and vomiting, headache, and flushing particularly after rapid infusion. Intravascular coagulation and thrombosis have been reported, mainly in patients with liver disease, and factor IX should be used with care in patients at risk of thromboembolism or disseminated intravascu-

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.