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-