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7 Procoagulators

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The factor concentrates discussed below are primarily obtained from clotting factors circulating in plasma. The factors enhancing coagulation are called procoagulators. Fibrin is formed from fibrinogen by activation of procoagulators. Fibrin consolidates the primary clot consisting of aggregated platelets.

The liver is predominantly the place of synthesis of procoagulatory clotting factors. With the exception of factors V, VIII and XIII, all procoagulatory clotting factors are so-called serine proteases (amino acid 'serine' at the active site) and circulate in the blood mostly in their inactive form (proenzyme).

Factor VII is also commercially available in its activated form (rFVIIa) as a genetically engineered preparation. There are no single-factor concentrates for factors II and X.

Furthermore, factors V and XI are currently not available in a highly concentrated form in Germany. Therefore fresh frozen plasma (FFP) is used in cases of factor V or XI deficiency relevant towards bleeding (see section 4.4.4.5).

Because of the clinical relevance the application of procoagulators in patients with acquired deficiency and bleeding complications is also discussed in the following sections, in particular in the sections 'Fibrinogen', 'Prothrombin Complex Concentrate' as well as 'Recombinant Factor VIIa'. Regarding the comprehensive management of these acutely ill patients, the reader is particularly referred to a recent review article by Mannucci and Levi [61].

7.1 Fibrinogen

7.1.1 Preparation, Quality Criteria

The starting material is pooled human plasma. Following the thawing and pooling of plasma, fibrinogen concentrate is obtained from cryoprecipitate (procedure according to Cohn/Oncley).

7.1.2 Active Constituents

The effective component of the only concentrate commercially available in Germany contains human fibrinogen (ratio of coagulable protein >80%), with human albumin added as stabilizer.

7.1.3 Physiological Function

Fibrinogen, a glycoprotein with a molecular weight of approximately 340,000 Da, is predominantly formed in the liver and stored in both endothelial tissue and platelets. Its biological half-life is 96–120 h. The normal fibrinogen concentration in plasma is 1.5–4 g/l, depending on the particular reference collective.

On the one hand, water-soluble fibrinogen is the substrate of plasmatic blood coagulation; on the other, it functions as an essential ligand in platelet activation and platelet aggregation. Fibrinogen is an acute phase protein; its concentration may rise rapidly within a few hours to more than 10 g/l during infections and postoperatively.

In pregnancy the physiological level of fibrinogen may rise to values up to 6 g/l.

7.1.4 Application

7.1.4.1 Congenital Fibrinogen Deficiency

Various congenital variants and disorders of fibrinogen formation (hypo- or dysfibrinogenemia) have been described [12, 68]. The individuals concerned may be asymptomatic or have a predisposition to thrombosis. Dysfibrinogenemia is rarely associated with a clinical disposition to bleeding.

The bleeding tendency in dysfibrinogenemia is usually mild but can be considerable during and after surgery or particularly post partum. Depending on the size of the wound surface, fibrinogen levels of at least 1 g/l (in cases of severe bleeding at least 1.5 g/l) are generally sufficient during elective surgery.

Congenital afibrinogenemia (i.e. no functional fibrinogen is detectable) must be associated with a severe bleeding tendency so that in individual cases even continuous prophylactic replacement may be indicated.

The widest clinical experience has been gained for years with applying fibrinogen concentrate for the treatment or prevention of bleeding in patients with congenital fibrinogen deficiency [13, 55, 69, 82, 91]. Due to the rarity and heterogeneity of these congenital defects, no controlled trials have been carried out.

7.1.4.2 Acquired Fibrinogen Deficiency

In daily clinical routine acquired fibrinogen deficiency following increased consumption is found in disseminated intravascular coagulation, loss and dilution coagulopathy [10, 22, 24, 30, 86]. Fibrinogen deficiency induced by increased turnover is also found in reactive or therapeutic hyperfibrinolysis [83]. Acquired fibrinogen deficiency due to impaired synthesis occurs in cases of severe damage of the liver parenchyma or following asparaginase therapy. In cases of pronounced damage of the liver parenchyma acquired dysfibrinogenemia may also occur. A distinctive fibrinogen deficiency may also occur in acute lymphoblastic leukemia, in particular acute promyelocytic leukemia, obstetric complications, burns, and states of shock with massive hemorrhage or distinctive disseminated intravascular coagulation (DIC) [26].

Acquired fibrinogen deficiency may also occur in isolated cases but is frequently accompanied by other hemostatic or fibrinolytic disorders.

A distinctive fibrinogen deficiency can develop in the event of massive transfusions in the context of loss and dilution co-

agulopathy, because primary replacement by crystalloids, colloids and possibly RBC concentrates is performed almost exclusively without plasma. In such situations fibrinogen levels are the first procoagulatory factors to decline, dropping to a critical range of 1 g/l. The other clotting factors and platelets decline later on, i.e. in cases of much more extensive blood loss, below critical threshold values [32, 35].

Severe liver disease with impaired synthesis primarily presents with a complex synthesis disorder of almost all of the proteins relevant for coagulation [79]. Although no trials have been conducted, the administration of FFP is therefore often recommended in cases of bleeding (see chapter 4). However, if a distinct deficiency in factors and cellular components has already developed due to blood loss, large amounts of FFP alone (1–1.5 l) cannot achieve sufficient hemostasis. Regarding fibrinogen, it must be noted that there is not only a drop in fibrinogen levels in severe liver damage, but that dysfibrinogenemia and hyperfibrinolysis may additionally occur. Critical threshold levels for the possible occurrence of spontaneous bleeding are approximately 1 g/l in these diseases.

Hyperfibrinolysis can occur in DIC as well as in multiple organ failure, in particular with liver damage but also as an isolated coagulation disorder (e.g. in resection of the prostate or in cardiac, pulmonary, pancreatic or uterine surgery). Not only is the generated fibrin destroyed by endogenous lysis, but also fibrinogen. The primary therapy consists of the interruption of fibrinolysis by antifibrinolytic drugs. The recommended course of action is the same in both therapeutically induced fibrinolysis and severe hemorrhage. Only in a persisting disposition to massive bleeding and low levels of fibrinogen (<1 g/l, measured not earlier than 8 h after the end of therapy), lysis should be interrupted and fibrinogen substituted.

In asparaginase therapy the synthesis of all aspartic acid-containing proteins is impaired. A decrease particularly of antithrombin levels but also of fibrinogen levels is to be anticipated. In the patients concerned thrombosis may occur (if antithrombin deficiency is dominant) and/or bleeding (if fibrinogen deficiency is dominant). In order to avoid these complications, it is reasonable to substitute the respective coagulation components that are lacking. The threshold value for intervention by fibrinogen substitution is also approximately 1 g/l or less. Irrespective of asparaginase therapy, a massive fibrinogen and platelet deficiency may develop in cases of acute leukemia, in particular acute promyelocytic leukemia. In complications during pregnancy and delivery (e.g. atonic uterus) rare but possibly fulminant defibrination syndromes may occur [51, 70].

7.1.4.3 Laboratory Diagnostics

The two screening tests prothrombin time (PT) and partial thromboplastin time (PTT) also detect fibrinogen. However, it must be pointed out that both tests distinctively demonstrate pathological values only in pronounced fibrinogen deficiency below the critical threshold value of 1 g/l. In cases of acute bleeding or relevant disposition to bleeding it is therefore recommended to determine fibrinogen concentrations directly (method according to Clauss). Furthermore, it must be pointed out that, following the application of colloids, a fibrin polymerization disorder in terms of a clinical disposition to bleeding may occur. In addition, false elevated fibrinogen values may be measured. The coagulometers measuring scattered light are widely used but are prone to measure false elevated fibrinogen values in plasma laced with colloids [36]. It must be ensured in the respective clinical unit that fibrinogen levels can be measured reproducibly and correctly in the range around and below 1 g/l (calibration, quality assurance).

To estimate fibrinogen turnover and synthesis, it may be reasonable to determine the D-dimer and/or a thrombelastogram in addition to fibrinogen concentrations.

7.1.5 Storage, Shelf Life and Package Sizes[*]

Fibrinogen concentrate should be stored at 4–8 °C. The shelf life amounts to 5 years. Ready-to-use solutions must be administered without delay, as they do not comprise of preservatives.

Fibrinogen: 1 g/50 ml dissolving agent or 2 g/100 ml dissolving agent.

Water for injection must be used as solving agent.

Note: According to the manufacturer, no dilution in glucose or sodium chloride solution should be performed.

7.1.6 Indications

7.1.6.1 Substitution in Congenital Fibrinogen Deficiency

Recommendations [19, 40, 55]:

- Prophylactic physician-controlled continuous therapy (home treatment) in severe congenital fibrinogen deficiency to prevent frequent recurrent bleeding episodes, during gravidity to maintain pregnancy, also in individual cases of hemorrhagic dysfibrinogenemia,
- Perioperatively and in surgical interventions with a risk of bleeding,
- Intermittently and prophylactically to prevent bleeding in known fibrinogen deficiency as well as in hemorrhagic dysfibrinogenemia (table 7.1).

7.1.6.2 Substitution in Acquired Fibrinogen Deficiency

General recommendations:

- The critical threshold values for the occurrence of spontaneous bleeding are <1 g/l (in severe hemorrhage 1.5 g/l).

[*] See section 0.4.

Table 7.1. Substitution therapy in congenital fibrinogen deficiency

Defect	Modality	
Congenital hypofibrinogenemia (fibrinogen level between 0.5 and 1.5 g/l), congenital, hemorrhagic dysfibrinogenemia	Generally no replacement therapy is necessary in congenital hypofibrinogenemia. Prior to surgery or to diagnostic interventions with an increased risk of bleeding (e.g. lumbar or epidural puncture and organ biopsies), a fibrinogen substitution is to be performed if fibrinogen levels <1 g/l. Fibrinogen levels of at least 1 g/l must be aimed for (in severe hemorrhage of at least 1.5 g/l).	1 C+
Congenital afibrinogenemia (no functional fibrinogen is found)	Prior to all surgical interventions the concentration of fibrinogen in plasma should be elevated to the reference range of at least 1 g/l (in severe hemorrhage of at least 1.5 g/l) and maintained in this range until wound healing. In rare cases a continuous prophylaxis may be necessary.	1 C+

– The fibrinogen level should always be specifically determined. An indirect determination using PT or PTT is not sufficient for any decisions regarding substitution therapy. The detection limit of the laboratory assay must be taken into account.
– The mean adult dose is around 3–5 g; following administration, the levels should be monitored and maintained above the critical threshold value (approx. 1 g/l).
– In hyperfibrinolysis or DIC the administration of fibrinogen is only indicated following interruption of the coagulation disorder by antifibrinolytic drugs or antithrombin in cases of persistent bleeding and low levels of fibrinogen.

Fibrinogen can be substituted perioperatively in interventions or lesions with the risk of acute bleeding and confirmed fibrinogen deficiency (massive transfusion, dilution and loss coagulopathy).	**2 C+**
Fibrinogen can be substituted in synthesis disorders (liver damage) with fibrinogen deficiency or in hemorrhagic dysfibrinogenemias as prophylaxis and therapy of hemorrhage and confirmed fibrinogen deficiency.	**2 C+**
Fibrinogen can be substituted as a prophylaxis and therapy of hemorrhage and confirmed fibrinogen deficiency of different origin (e.g. acute leukemia, asparaginase therapy, obstetrical complications, postoperatively).	**2 C+**

*7.1.7 Dosage**

The required fibrinogen dose is estimated from the plasma volume (≈ 40 ml/kg body weight) according to the following formula:

$$\text{Fibrinogen dose (g)} = \text{desired increase (g/l)} \times \text{plasma volume (l)} \quad (1).$$

Following fibrinogen substitution, the minimum plasma concentration should be 1.0 g/l plasma. In adults single doses of 3–6 g are usually required [82].

Note: Administration of 3 g of fibrinogen in a volume of 3 l plasma increases fibrinogen levels by approximately 1 g/l. In congenital deficiency the half-life (96–120 h) must be considered. When the half-life is shortened, fibrinogen levels should be monitored more frequently.

7.1.8 Absolute and Relative Contraindications

Overt thrombosis and myocardial infarction preclude fibrinogen use except in cases of life-threatening hemorrhage.

In DIC fibrinogen substitution is dangerous because during ongoing fibrin generation it can augment fibrin formation in the microcirculation and thus further the risk of multiple organ failure. Administering fibrinogen is thus indicated only when active intravascular coagulation has ceased and/or when appropriate therapeutic, particularly anticoagulatory, measures have already reduced fibrin turnover in the hemostatic system.

7.2 Prothrombin Complex Concentrates– Prothrombin (Factor II), Proconvertin (Factor VII), Stuart Factor (Factor X) and Antihemophilic Factor B (Factor IX)

7.2.1 Preparation, Quality Criteria

Factors II, VII, IX and × of the prothrombin complex as well as the proteins C, S and Z are isolated from large cryoprecipitate-poor plasma pools, using ion exchange chromatography in combination with various precipitation and adsorption methods.

Prothrombin complex concentrates (PCC; in German PPSB = *P*rothrombin (factor II), *P*roconvertin (factor VII), *S*tuart factor (factor X) and antihemophilic factor *B* (factor IX)) are standardized with respect to their content in factor IX. Because of the varying recovery and stability of factors II, VII, IX and X during successive production steps, the composition of clotting factor activities in the concentrates inevitably deviates from physiological conditions. Thus the amount of

* See section 0.4.

prothrombin and factor X may be double, whereas factor VII may measure only half the activity of factor IX. Protein C, S and Z content similarly exhibits a large range of variation.

Activated clotting factors and activated protein C or plasmin are virtually no longer contained in currently available PCC preparations, so that adverse reactions such as thromboembolic episodes, DIC, and/or hyperfibrinolytic bleeding are extremely unlikely, even when larger doses are administered [33, 49, 87]. Thromboembolic events reported to have occurred in the past following application of PCC mainly occurred in patients with hemophilia B, liver disease and/or antithrombin deficiency, particularly following repeated high-dose administration [49]. A distinct prothrombin overload in some PCC which are no longer commercially available is most likely a cofactor in resultant thromboembolic complications [29]. Batch control performed by the Paul-Ehrlich-Institute ensures today's high safety standard. Therefore, no general antithrombin substitution is required. According to the rules and regulations of the European Pharmacopeia, all preparations contain heparin (up to 0.5 U/U factor IX) and some contain antithrombin as well (1–2 U/ml) [56, 76].

7.2.2 Active Constituents

Prothrombin complex concentrate contains a number of proenzymes (zymogens) of factors of the prothrombin complex, namely the human clotting factors II (prothrombin), VII (proconvertin), X (Stuart-Prower factor), IX (antihemophilic globulin B) as well as the inhibitor protein C, its cofactor protein S and the coagulation regulator Z. This mixture is also known as PCC.

7.2.3 Physiological Function

The clotting factors II, VII, IX and X (prothrombin complex) stimulate coagulation while proteins C and S inhibit it. Protein Z is a plasma protein dependent on vitamin K, and represents a cofactor for inactivation of factor X by a protease inhibitor dependent on protein Z. All seven proteins are synthesized in the hepatocytes. Sufficient concentration of intracellular vitamin K and an intact vitamin K metabolism are required for their biosynthesis.

Congenital factor II, VII, IX and X deficiencies predispose the patient to bleeding, depending on the location of the genetic defect, while in contrast congenital protein C and S deficiencies predispose to thromboembolic disorders.

Homozygous carriers of factors II, VII, and X deficiencies are characterized by reduced activity of single factors (<10%), whereas in heterozygous carriers, activity is reduced by 10–50%. Homozygous carriers of factor deficiencies have a strong propensity to bleeding. Heterozygous carriers of factors II, VII and X deficiencies may be devoid of clinical symptoms, but may be endangered during surgery and in cases of accidents.

Congenital homozygous deficiency of protein C or S is associated with a considerable risk of thromboembolism (Purpura fulminans) as early as during the first year of life. Heterozygous deficiencies can remain clinically inconspicuous for long periods of time.

An acute or chronic acquired reduction of factors belonging to the prothrombin complex may be caused by loss or dilution, consumption or limited synthesis. Synthesis of factor V, antithrombin, proteins C, S and Z as well as of other clotting factors and inhibitors may additionally be diminished to various degrees. In cases of acute liver failure, not only is a diminished synthesis observed, but a defective synthesis is to be anticipated along with elimination disorders [80].

If vitamin K is deficient, or if following ingestion of a vitamin K antagonist, the liver cells cease to produce mature clotting factors of the prothrombin complex, a deficiency of plasma factors II, VII, IX, X as well as of proteins C, S and Z may result.

When coumarin derivatives are used for oral anticoagulation, the fact that the synthesis of the four clotting factors depends on sufficient amounts of vitamin K is used therapeutically for prophylaxis of thromboembolic events: the ingestion of such vitamin K antagonists reduces the clotting potential to such an extent that the patients concerned no longer have an increased risk of thrombosis, while the induction of an increased risk of bleeding is also prevented for as long as possible. PCC is used for the short-term specific replacement of vitamin K-dependent clotting factors under the following circumstances: severe bleeding complications caused by overdosing, urgently necessary surgical interventions as well as accidents resulting in severe bleeding.

Half-lives of clotting factors are as follows:

- Prothrombin 48–60 h
- Factor VII 1.5–6 h
- Factor IX 20–24 h
- Factor X 24–48 h
- Protein C 1.5–6 h
- Protein S 24–48 h
- Protein Z 24–48 h.

These half-lives may be considerably shorter during pronounced catabolic states, in severe liver damage, and in DIC. Low-dosed administration of recombinant factor VIIa is an effective alternative.

*7.2.4 Storage, Shelf Life and Package Sizes**

PCC currently commercially available are to be stored at a maximum temperature of 25 °C or at 2–8 °C. The ready-to-use solution must be administered immediately. Longer lifetimes of the reconstituted solutions must be avoided for ste-

* See section 0.4.

rility reasons and possible instability of the clotting factors. Attention should be paid to the product information leaflets by the manufacturer.

PCC is available in lots of 200, 250, 300, 500 or 600 U, relating to the factor IX content in the product. Most manufacturers provide the content levels of activated factors II, VII, X and of proteins C and S either based on the specific batch or as average values.

7.2.5 Indications and Dosage

Prospective clinical studies for the indications provided are scarcely available. The following recommendations can be provided on the basis of these few studies and of long years of clinical experience:

- In cases of severe liver damage, in disseminated intravascular coagulation and loss or dilution coagulopathy, the prothrombin complex deficiency may be pronounced to such a degree that in addition to FFP infusion (see chapter 4) substitution with PCC is required [33].
- While under oral anticoagulation therapy, PCC therapy is the preferred treatment together with vitamin K in patients with episodes of major bleeding, in urgent essential surgery and emergencies [15, 21, 72, 74]. FFP should only be used in cases where PCC is unavailable or contraindicated (e.g. in known heparin-induced thrombocytopenia type II).
- Replacement with clotting factor concentrates is not always necessary in factor II, VII, IX and X deficiencies. Depending on the cause, localization and extent of manifest or imminent bleeding, other therapeutic measures (e.g. vitamin K substitution, inhibition of activation of the clotting system or of hyperfibrinolysis) are primarily indicated [33].
- PT is suitable as a screening test. This can also be used for follow-up control. FFP serves as second-line therapy in complex hemostatic disturbances.

It is essential for all indications: Following dissolving the lyophilisate, PCC is administered as an i.v. infusion according to the specifications in the expert information (Summary of Product Characteristics).

7.2.5.1 Congenital Prothrombin Complex Factor Deficiency

In congenital deficiency PCC can be administered for the cessation of spontaneous, traumatic and perioperative bleeding when insufficient factor activity prevents hemostasis.	**2 C+**
In congenital deficiency PCC can be administered to prevent bleeding in cases of factor deficiencies, during and after surgery to ensure wound healing and, in individual cases, as prophylactic long-term treatment.	**2 C+**

Note: Hemophilia B (factor IX deficiency) and congenital factor VII deficiency should always be treated with the respective single factor concentrates. Exceptions: PCC may be employed in emergencies only when factor IX or factor VII concentrates are not available.

Dosage in congenital deficiencies: Dosage and duration of replacement therapy depend on the severity of the disorder, its localization and the extent of bleeding.

As a rule, 1 U of PCC/kg body weight increases the activity of factors VII and IX by 0.5–1% and the activity of factors II and X by 1–2%. 1 U PCC/kg body weight increases the thromboplastin time by approximately 1%.

Depending on each case, the maintenance dose may be half of the initial dose. The respective half-lives as well as minimum activities required for hemostasis should be taken into account.
High initial doses of 40 U/kg body weight are indicated in:

- life-threatening or extensive bleeding (e.g. cerebral bleeding, bitten tongue, retroperitoneal bleeding, compartment syndrome, muscle bleeding, gastrointestinal bleeding and oral cavity bleeding),
- surgery involving large wound surfaces and/or danger of extensive bleeding (including tonsillectomy).

Doses of more than 40 U/kg body weight should be administered as several partial doses.
Low initial doses of 20 U/kg body weight are indicated in:

- minor skin, muscle and joint bleeding,
- epistaxis,
- hematuria and
- surgery involving small wound surfaces (e.g. tooth extraction, herniotomy).

After application of the initial dose, activity of deficient clotting factors should be repeatedly determined in order to monitor the therapeutic outcome and to establish a firmer base for further treatment.

In addition to procoagulator therapy, vitamin K should be substituted.

7.2.5.2 Acquired Prothrombin Complex Factor Deficiency

In cases of bleeding or for perioperative replacement in surgery involving an increased risk of bleeding PCC is indicated in patients with single or multiple prothrombin complex factor deficiencies when the residual activity of factors II, VII, IX or X or prothrombin time is below 40% (INR > 2):

- in cases of overdosing oral vitamin K antagonists (PT in% below therapeutic level, INR above therapeutic level) or at discontinuation of therapy with oral anticoagulants in emergencies (e.g. non-elective surgery),
- in severe liver disease as well as during and following liver transplantation. In these cases complex impairment of hemostasis is to be considered (see chapter 4),
- in vitamin K deficiency (e.g. high-dose antibiotic therapy, persisting diarrhea, resorption disorders) with life-threatening bleeding,

– in life-threatening bleeding in neonates or infants with severe vitamin K deficiency.

Dosage in acquired deficiencies: Dosage and duration of replacement therapy depends on the severity of the hemostatic disorder, localization, extent of bleeding as well as the clinical situation [9, 33, 83].

Prior to administering PCC, clotting analyses are to be performed, provided that the patient's condition permits this. To estimate both initial and maintenance doses, the determination of the PT is required.

However, considerable individual variation may occur and the reference values provided here may not be reached. In cases of severe bleeding initial bolus doses of 20–25 U/kg body weight are recommended.

In cases of slight bleeding, slight injury or minor surgery, factor activities of 20–40% are sufficient (corresponding to a PT value of 30–50%), whereas in severe injury or major surgery factor activities of 50–60% (PT value 60–80%) should be maintained. Higher factor activities may be necessary in individual cases.

30–60 min following the first application a further clotting analysis is necessary. Indication and dosage of further PCC administration depend on the patient's condition and laboratory results.

7.2.5.3 Interrupting the Effects of Vitamin K Antagonists

Bleeding that occurs during anticoagulation therapy with coumarin derivates may be caused either by overdose of anticoagulants or by displacement of the coumarin derivates from albumin binding by other medication, leading to an increase in the concentration of free (and therapeutically effective) coumarin in patients' plasma. Moreover, decreased synthesis of clotting factors in liver disease (e.g. acute hepatitis) can reinforce the effect of anticoagulation therapy with coumarin derivates. Bleeding often results spontaneously from initially minimal lesions.

Therapy consists of:

– Discontinuing anticoagulants.
– Administering vitamin K (10–20 mg) to reverse the effect of anticoagulants.
– PCC is indicated only in cases of acute life-threatening bleeding and emergency surgery. PCC has the advantage of normalizing the clotting defect in the shortest possible time.
– Administration of low-dose anticoagulants that are immediately effective (also monitoring of the antithrombin level) in the event that anticoagulation must be continued.

For decisions regarding therapy and for follow-up control, the PT should be determined. Regarding the dosage according to the desired PT value (30–50% in slight bleeding, 60–80% in severe bleeding), refer to section 7.2.5.2.

In the course of further therapy the half-life of coumarin derivates used (Warfarin 48 h, Marcumar 7 days) should be taken into account. Following further decline of the PT value, additional administration of vitamin K or PCC should be considered.

Table 7.2. Recommended dosage

	Prothrombin time in INR (at the onset of treatment)		
	2.0–3.9	4.0–6.0	>6.0
Dosage (factor IX/kg body weight)	25	35	50

When INR is referred to in decisions on treatment and follow-up control, the recommendation as stated in table 7.2 applies for the normalization of INR (PT in INR <1.3).

A maximum dose of 5,000 U should not be exceeded. Level of evidence regarding indication in acquired deficiency is given in table 7.3.

7.2.6 Absolute and Relative Contraindications

– DIC.
– PCC is indicated in DIC with overt bleeding caused completely or partially by prothrombin complex factor deficiency, and only if the cause of the DIC is also being treated. In DIC PCC preparations should not be administered without monitoring and possibly normalizing the antithrombin level [50].
– Heparin-induced thrombocytopenia type II, as almost all PCC contain heparin (*exception:* currently in Europe only one heparin-free PCC containing antithrombin is commercially available in the Netherlands).
– During pregnancy and lactation PCC should only be used following careful consideration.
– Caution is advised for patients with known sensitivity to compounds contained in the preparation.

7.3 Factor VII Concentrate

7.3.1 Preparation, Quality Criteria

Factor VII is isolated from large cryoprecipitate-poor plasma pools using ion exchange chromatography and adsorption to aluminum hydroxide. The only factor VII concentrate commercially available in Germany is standardized regarding its factor VII contents. The clotting activity is given as International Units (U).

7.3.2 Active Constituents

The only concentrate commercially available in Germany contains the proenzyme (zymogen) factor VII that is part of the prothrombin complex (see section 7.2.2).

Table 7.3. Level of evidence regarding indication in acquired deficiency

Indication	Level of evidence	Comments
PCC shall be administered in order to achieve hemostasis in cases of severe bleeding during therapy with vitamin K antagonists. Prior to non-elective major surgery or in trauma (cases of emergency), PCC should be administered as a bleeding prophylaxis	1 B	vitamin K as supplement
In liver damage PCC could be administered in order to halt bleeding	2 C	FFP as second-line therapy
In acquired deficiency of prothrombin complex PCC could be administered in order to halt bleeding	2 C	vitamin K as supplement

7.3.3 Physiological Function

Clotting factor VII is effective as a procoagulator and is synthesized in the hepatocytes. A sufficient intracellular vitamin K concentration is necessary for its biosynthesis (see section 7.2.3).

7.3.3.1 Congenital Factor VII Deficiency

Depending on the autosomal recessive genetic defect and the related decrease in factor VII activity, congenital factor VII deficiency predisposes to bleeding.

Homozygous carriers of factor VII deficiency are characterized by a lower activity level (<10%) while heterozygous carriers show decreased activity levels of between 10 and 50%. Although on average factor VII activities are lower in patients with a strong propensity for bleeding, this does not permit any prediction regarding a particular patient's disposition to bleeding. Thus, there are asymptomatic patients who demonstrate only a few percent of residual factor VII activity as well as symptomatic patients demonstrating an activity of around 50% [62]. PT values may even be marginal or only slightly lower.

Heterozygous genetic carriers of the factor VII deficiency may be without pathological findings; however, they are at risk of bleeding in the event of surgery or trauma.

The mean half-life of factor VII following substitution is 5 h [75].

*7.3.4 Storage, Shelf Life and Package Sizes**

Factor VII concentrate is generally stored at 2–8 °C. The ready-to-use solution should be administered immediately. Longer lifetimes of the reconstituted solutions must be avoided for sterility reasons and possible instability of the clotting factors. Attention should be paid to the product information leaflets provided by the manufacturer.

Package size is 600 U referring to the factor VII content of the preparation.

7.3.5 Application

7.3.5.1 General Remarks

Following reconstitution of the lyophilisate, the factor VII concentrate is very slowly infused intravenously.

There are no prospective clinical trials on the indications listed here. Based on long-term clinical experience, the following recommendations are possible.

7.3.5.2 Congenital Factor VII Deficiency

- Treatment of bleeding disorders that were caused by isolated congenital factor VII deficiency.
- Prophylaxis of bleeding disorders that could be caused by isolated congenital factor VII deficiency.

Note: Congenital factor VII deficiency should now only be treated with highly purified plasmatic or recombinant single factor concentrates. Only in emergencies in the absence of the availability of single factor concentrates is the administration of PCC advisable.

*7.3.6 Dosage**

Dose and duration of the substitution therapy depends on the severity of factor VII deficiency as well as on the site and extent of bleeding and the clinical condition of the patient.

An International Unit (U) of factor VII activity corresponds to the activity of factor VII in 1 ml of normal human plasma (= 100%).

The calculation provided below regarding the factor VII dose required is based on the empirical finding that 1 U of factor VII/kg body weight increases factor VII activity in plasma by approximately 1.7% referred to the normal activity.

The dose required is determined using the following formula:

$$\text{Dose U} = \text{body weight (kg)} \times \text{desired increase in factor VII levels (\%)} \times 0.6 \quad (2)$$

* See section 0.4.

Table 7.4. Administration of factor VII in cases of bleeding or in surgical interventions

Grade of bleeding/type of surgical intervention	Factor VII activity levels desired, U/ml	Duration of therapy
Minor bleeding	0.10–0.20	a single dose
Major bleeding	0.25–0.40	for 8–10 days or until healing is completed**
Minor surgical interventions	0.20–0.30	a single dose prior to intervention or, in case the bleeding risk is assumed to be higher, until wound healing is completed
Major surgical interventions	preoperative > 0.50 then 0.25–0.45	for 8–10 days or until healing is completed**

**Based on clinical assessment, lower doses may be sufficient in individual cases towards the end of therapy, provided adequate hemostasis is achieved.

The dose and the dosing interval should always be based on the clinical outcome in each individual case.

In patients with congenital factor VII deficiency the administration of factor VII in the event of hemorrhage or of surgical interventions shall be performed in accordance with table 7.4.	**1 C+**

Dosing intervals have to be adjusted to the short half-life of factor VII in circulation amounting to approximately 3–5 h. Accordingly, the interpretation of levels in plasma must be performed with the full awareness of the precise time of administration (peak level – trough level).

In individual cases of congenital factor VII deficiency (severe factor VII deficiency) administration shall be performed as a prophylaxis.	**1 B**

7.3.7 Absolute and Relative Contraindications

- Factor VII concentrate must be applied with caution in patients with known intolerance to components in the product.
- Factor VII concentrate should be applied only following careful consideration during pregnancy and lactation.

7.4 Recombinant Factor VIIa

7.4.1 Preparation, Quality Criteria

Recombinant factor VII (rFVII) is obtained from cDNA from the human factor VII codon using baby hamster kidney cells. Activation of the single-chain rFVII to double-chain rFVIIa is done by hydrolytic cleavage between positions 152 (arginine) and 153 (isoleucine) of the peptide chain. rFVIIa concentrate does not contain any other activated clotting factors. Further purification of rFVIIa includes several chromatography steps as well as virus inactivation. The purified product is then portioned and lyophilized.

7.4.2 Active Constituents

Eptacog alfa (activated) is recombinant clotting factor VIIa (rFVIIa) with a molecular weight of around 50,000 Da. Following reconstitution 1 ml of solution contains 0.6 mg of Eptacog alfa (activated). Additional ingredients: sodium chloride, calcium chloride dihydrate, N-glycylglycine, Polysorbate 80, mannitol).

The excipients used have no pharmacological effects.

7.4.3 Physiological Function and Pharmacological Effect

Under physiological conditions only 1% of factor VII in its activated form circulates in the blood. By injecting a pharmacological bolus dose of factor VII in its activated form, the factor VIIa concentration is briefly increased numerous times over normal physiological concentrations so that a maximum number of TF (tissue factor) molecules form complexes with factor VIIa. In doing so, an activation of the clotting system is achieved that is limited to the site of trauma. The supraphysiological factor VIIa level in the blood also has the effect that factor VIIa binds to activated platelets with a lower degree of affinity. In addition, factor VIIa activates factor X to factor Xa, irrespective of the presence of TF. As a consequence, thrombin formation is accelerated and amplified. Thrombin formation is able to compensate a deficiency in factor VII, factor IXa-VIIIa complex, or factor Va-Xa complex. Thus a pathway for the initiation of coagulation is formed that is independent of a sufficient activation of factors IX and/or VIII.

Due to the lower affinity of factor VIIa to activated platelets, a supraphysiological (pharmacological) dose of rFVIIa is necessary to achieve hemostasis.

In contrast, FVIIa has almost no affinity at all to inactive platelets, which may be the reason for the lack of any relevant systemic clotting activation by supraphysiological doses of factor VIIa [31, 42].

7.4.4 Storage, Shelf Life and Package Sizes[*]

Recombinant factor VIIa must be stored at 2–8 °C. The preparation is commercially available in three sizes: 1.2 mg, 2.4 mg, and 4.8 mg. The units are specific for rFVIIa and incomparable with units of other clotting factors. Shelf life is 3 years. Following reconstitution, rFVIIa may be stored at 2–8 °C for 24 h.

7.4.5 Licensed Indication and Dosage

General recommendation: The following preconditions apply for the administration of rFVIIa: a fibrinogen level of ≥1 g/l, a platelet count of ≥50,000 (or better ≥100,000) × 10^9/l and a pH value of ≥7.2 [63, 92].

7.4.5.1 Bleeding and Prevention of Bleeding in Patients with Inhibitors in Congenital Hemophilia A

An intravenous bolus dose of 90 μg/kg body weight is recommended as an initial and maintenance dose. The bolus injection should be administered over a period of 2–5 min. Due to the short half-life of rFVIIa, therapy intervals are initially 2–3 h until hemostasis is achieved. In individual cases a shorter interval may be necessary. If therapy is to be continued, therapy intervals can be prolonged gradually to 4 and up to 12 h, provided the continued treatment is indicated [1, 5, 31, 60, 78, 85].

In individual cases (e.g. in children who have a higher clearance compared to adults [93]) a higher dosage may be necessary. No maximum daily dose for rFVIIa is specified, as e.g. for activated prothrombin complex preparations. rFVIIa may also be administered on an outpatient basis.

In the event of bleeding in hemophilic patients with clotting factor VIII or IX inhibitors, rFVIIa shall be administered at a dose of 90–120 μg/kg body weight as bolus in 2- to 3-hour intervals until hemostasis is achieved. It is also possible to administer a single injection of 270 μg/kg body weight.	**1 C+**

Due to the shorter half-life of rFVIIa in children, it may be reasonable to increase the dosage levels up to threefold the initial concentration. In clinical trials a dose of up to 270 μg/kg body weight per bolus was found to be safe and at least equal to the repetitive administration of 90 μg/kg body weight. Based on data from trials which included children and adults, it may be expected that the number of necessary venous injections can be reduced by a single bolus megadose [45, 46, 78]. A randomized multicenter double-blind prospective trial on patients with frequently recurring bleeding could demonstrate that the frequency of bleeding episodes was markedly reduced by a dosing regimen of 90 μg/kg body weight per day or 270 μg/kg body weight, compared to the frequency prior to prophylaxis onset [52].

In the event of bleeding in hemophilic children with clotting factor VIII or IX inhibitors, rFVIIa shall be administered at a dose of 90–270 μg/kg body weight as bolus in 1.5- to 2-hour intervals until hemostasis is achieved.	**1 C+**

7.4.5.2 Bleeding and Prevention of Bleeding in Patients with Acquired Inhibitors against Clotting Factors

In patients with inhibitors in acquired hemophilia A, spontaneous autoantibodies to factor VIII occur and, in rare cases, to other clotting factors. The highest incidence has been observed in pregnant women, particularly during postpartum, and in older patients in their early seventies. Gender does not play a significant role in the incidence of autoantibodies. In sudden severe bleeding events the laboratory parameters which determine the course of treatment are a prolonged activated PTT and, on performing further diagnostics, a positive plasma exchange test. In these patients it is necessary to initiate treatment without delay, in particular *prior* to commencing any surgical interventions [1, 5, 6, 31].

In the event of severe bleeding episodes in patients with inhibitors in acquired hemophilia A, rFVIIa shall be administered at a dose of 90–120 μg/kg body weight as bolus in 2- to 3-hour intervals until hemostasis is achieved.	**1 C+**

factor VIII inhibitor bypassing activity (FEIBA) can also be used as an alternative treatment of inhibitors in acquired hemophilia A (see section 6.1.4). Regarding dosage, the reader is referred to the recommendations for patients with congenital hemophilia and inhibitors in section 6.5.3.3, subsection 'Treatment of Acute Bleedings (Children and Adults)'.

[*] See section 0.4.

7.4.5.3 *Bleeding and Prevention of Bleeding in Patients with Glanzmann's Thrombasthenia with Antibodies to Glycoprotein IIb/IIIa and/or HLA and with Former or Current Refractoriness to Transfusion of Platelet Concentrates*

rFVIIa has successfully been used in achieving hemostasis in patients with severe congenital or acquired allo- or autoantibody-induced thrombopathies and thrombopenias [34].

In patients with Glanzmann's thrombasthenia and severe bleeding a bolus dose (80–120 µg/kg body weight) shall be administered three times in the course of 2 h.	**1 C+**

Distinctive secondary bleeding episodes have been observed despite primary hemostasis in cases where no treatment with rFVIIa was conducted [71].

There are also anecdotal reports on positive clinical experiences with rFVIIa in patients with Bernard-Soulier syndrome, storage pool disease [4] and immunothrombopenia [17, 34, 94].

In patients with congenital thrombopathies such as e.g. Bernard-Soulier syndrome, storage pool disease and severe bleeding the administration of rFVIIa at a bolus dose of 90–120 µg/kg body weight could be indicated.	**2 C**

Bleeding has been frequently observed to cease following 1 or 2 injections.

7.4.5.4 *Bleeding and Prevention of Bleeding in Patients with Congenital Factor VII Deficiency*

Investigations on patients with congenital factor VII deficiency have demonstrated that rFVIIa should be generally administered at a dose of 15–30 µg/kg body weight as bolus every 6 h until hemostasis is achieved, provided that activity levels <10% and in the event of bleeding. The time interval until the next bolus can be prolonged during the course of treatment, depending on the bleeding pathology. In many instances a subsequent injection regime of twice a day is sufficient [41, 62].

In patients with congenital factor VII deficiency rFVIIa shall be administered at a dose of 15–30 µg/kg body weight as bolus every 6 h. Administration can also be performed as a prophylaxis.	**1 C+**

7.4.6 *Off-Label Use*[*]

Significant effects of rFVIIa administration (200 µg/kg body weight followed by 2 additional bolus doses of 100 µg each/kg body weight after 1 and 3 h) have been observed in a placebo-controlled phase II trial in patients with severe bleeding following blunt trauma. Transfusion requirements of RBC concentrates decreased significantly, and the frequency of massive transfusions as well as the rate of acute respiratory distress syndrome (ARDS) compared to placebo were significantly reduced. In open trials on the use of rFVIIa in case of massive bleeding [28, 47, 63] 71 trauma patients received mean rFVIIa doses of 90–140 µg/kg body weight per patient using an average of 1.6 bolus injections.

In patients with life-threatening postpartum hemorrhage rFVIIa has led to hemostasis in a number of cases after all other conservative and surgical conventional hemostatic therapies had failed [2, 11, 37], and in one case it was also possible to avoid a hysterectomy. In the majority of cases one or two rFVIIa bolus doses of approximately 20–120 µg/kg body weight were applied.

In several large case studies involving patients with bleeding complications following cardiac surgery, rFVIIa has led to hemostasis after all other conservative and surgical conventional hemostatic therapies had failed [43, 95]. In most cases rFVIIa was administered as a bolus at a dose ranging between 30 and 90 µg/kg body weight.

In case reports and in a controlled trial patients with hematologic oncologic diseases with severe bleeding episodes that were refractory to conventional therapy received rFVIIa; this also included patients following stem cell or bone marrow transplantation [67]. The mean single dose was observed to be just under 90 µg/kg body weight. A recent review article [23] states that bleeding has been halted in many patients following the first injection.

In individual cases of drug-induced life-threatening bleeding (due to factor IIa, factor Xa inhibitors, glycoprotein IIb/IIIa inhibitors), following the failed application of other procoagulatory substances, an administration of rFVIIa may be considered at a dose of 90–120 µg/kg body weight per bolus [8, 38, 88].

7.4.7 *Adverse Reactions*

A risk of thromboembolic events is involved in the employment of genetically engineered activated clotting factor VII (rFVIIa). Such adverse reactions have very rarely been observed (<1:25,000 standard doses) [1] when using rFVIIa as its only indication licensed to date: patients with inhibitors in hemophilia A (see chapter 11). Corresponding clinical trials on

[*] The legal issues involved in the off-label use are pointed out in section 0.4.

children demonstrated no increased rate of thromboembolic complications compared to conventional doses, even when using doses of 270 µg/kg body weight [45, 46, 78].

Due to the ongoing controversies regarding the statistical methods used [3, 58, 66, 90], no ultimate assessment of the registry data published on thromboembolic complications is possible. Thromboembolic events have occurred in the arterial and venous vascular system or in vessels damaged perioperatively or by trauma, in particular in patients receiving rFVIIa for non-licensed indications. Therefore the well-known adverse reactions of rFVIIa have to be specifically pointed out during the informed consent consultation between the physician and the patient, in particular if the preparation is used accordingly. For an assessment of off-label use of rFVIIa in acute blood loss the reader is referred to an exemplary review article [61].

7.4.8 Absolute and Relative Contraindications

Simultaneous or almost simultaneous administration of rFVIIa and activated PCC should only be performed following a strict risk-benefit analysis. The thrombogenic effect of activated PCC can thus be potentiated by simultaneous application of rFVIIa. In individual cases a temporary combined [48] or sequential application [18, 81] of rFVIIa and FEIBA was reported in hemophilia patients with inhibitors with a severe course of the disease who had demonstrated massive bleeding refractory to treatment. However, grave thromboembolic complications have been observed to occur in one patient [77]. Therefore, the decision regarding the combined use of these preparations must be made individually and be adjusted to the clinical course.

A known intolerance against murine, hamster or bovine protein can be a contraindication.

7.5 Factor XIII Concentrate

7.5.1 Preparation, Quality Criteria

The starting material is derived from pooled human plasma. The production is performed according to the Cohn/Oncley procedure. Following the separation of the cryoprecipitate and adsorption of the vitamin K-dependent factors of the prothrombin complex, the only factor XIII concentrate commercially available in Germany is obtained by precipitation with ethanol.

7.5.2 Active Constituents

The product contains fibrin-stabilizing factor XIII as its active component, namely both subunit factor XIII A (containing activity) and subunit factor XIII B (carrier protein); human albumin, sodium chloride, and glucose are added as stabilizers.

7.5.3 Physiological Function

Activated factor XIII (fibrin-stabilizing factor XIII) is a transglutaminase which cross-links fibrin covalently in the presence of calcium ions, thus increasing the mechanical firmness so that a firm three-dimensional fibrin net is formed, resulting in definite hemostasis. In doing so, factor XIII integrates alpha-2 antiplasmin and fibronectin into the clot, thus protecting it on the one hand against premature fibrinolysis and, on the other, serving as chemical lead for fibroblasts immigrating into the wound area. Longitudinal interlinking of the fibrin strands occurs quite rapidly while transversal interlinking representing the actual mechanical stabilization takes several hours. In blood factor XIII is activated by thrombin and binds to fibrinogen, but more strongly to fibrin. Factor XIII is found in plasma, platelets and certain tissues. Its plasma concentration amounts to 22 mg/l; the biological half-life is about 96–120 h. Factor XIII plays a physiological role in hemostasis, wound healing and in the maintenance of pregnancy during the first weeks after conception.

In the low concentration range the bleeding tendency correlates largely with the degree of factor XIII deficiency. Patients with severe congenital factor XIII deficiency particularly tend to experience umbilical cord stump hemorrhage, impaired wound healing, and intracranial bleedings; women have a tendency towards habitual abortion. As in hemophilia, skin, mucous membrane, soft tissue and joint bleedings occur also. In general, there is no spontaneous bleeding tendency in congenital deficiency and when factor XIII levels exceed 7% of the normal values. However, single cases of severe hemorrhage and impaired wound healing have been observed in heterozygote patients with factor XIII levels of around 50%, following surgery or trauma.

Acquired factor XIII deficiency is not rare. It may be caused by increased turnover (e.g. following intravascular clotting, sepsis, inflammatory intestinal diseases, systemic hematological disorders, increased blood loss, hyperfibrinolysis), by increased consumption (e.g. in major surgery) or by reduced synthesis (e.g. in liver disease). In patients with pre-existing coagulation activation prior to surgery (e.g. in tumor patients) a severe factor XIII deficiency might develop during surgery and thus cause massive intraoperative hemorrhage [19, 53, 96]. A typical symptom of a postoperative factor XIII deficiency is scattered secondary hemorrhage several hours following surgery, whereas hemostasis during surgery was observed to be completely normal. In addition to severe hemorrhage, acquired factor XIII deficiency may also induce acute postoperative impaired wound healing. This becomes usually apparent 3–7 days following surgery. Chronic wounds such as venous ulcers (ulcus cruris) or decubitus ulcers may also be linked with factor XIII deficiency.

A rare occurrence is inhibitor (antibody) formation in congenital factor XIII deficiency following replacement therapy or as autoantibodies [19].

Factor XIII is *not* determined by the screening tests PT and PTT because these tests only measure the point in time of onset of fibrin formation but not fibrin interlinking. The suspected diagnosis of factor XIII deficiency should be investigated further by laboratory tests in all cases of bleeding of unknown origin, especially in postoperative scattered secondary hemorrhage several hours following surgery or in intraoperative hemorrhage occurring in patients with activated coagulation.

7.5.4 Storage, Shelf Life and Package Sizes[*]

Factor XIII concentrates should be stored at 4–8 °C in the closed cardboard box. The shelf life is 3 years and is indicated on the box and the container. Ready-to-use solutions should be administered immediately, as there are no preservatives included.

Factor XIII concentrate: 250 U/4 ml; 1,250 U/20 ml.

*7.5.5 Range of Application, Dosage, Mode of Administration**

Congenital factor XIII deficiency: Due to the rarity of the disease, there is only a limited clinical knowledge available. Indications are prevention and therapy of hemorrhage and impaired wound healing. Controlled studies do not exist due to the rarity of these congenital defects (table 7.5).

Acquired factor XIII deficiency: Consumption of factor XIII may develop in the context of hemostasis and wound healing during and following major surgery (e.g. in general and abdominal surgery or cardiac surgery) [16, 79]. The extent of the decline in factor XIII concentration is also crucial while there is no clearly defined critical threshold either for hemorrhage or for impaired wound healing. In patients with factor XIII deficiency undergoing coronary surgery substitution leads to a significant reduction of drainage volumes and the extent of blood transfusion [27].

In patients with coagulation activation prior to surgery, caused by e.g. a malignant process, factor XIII deficiency becomes manifest intraoperatively rather than postoperatively through secondary bleeding [53, 96].

In patients with therapy-refractory postoperative wound healing disorders and factor XIII deficiency (level <70%), factor XIII substitution leads to a significant improvement of wound healing, potentially leading to complete healing [64] according to several controlled randomized double-blind trials. In chronic wounds (e.g. venous ulcers or decubitus ulcers), factor XIII therapy has also led to significantly improved healing [7, 97] while the best results were achieved with topical application which is not licensed in Germany [98].

Table 7.5. Substitution therapy in congenital factor XIII deficiency

Defect	Modality
Severe congenital factor XIII deficiency	Factor XIII concentration must be elevated and maintained within the reference range (>50%) prior to all surgical procedures until wound healing is complete. Prophylactic continuous therapy is recommended only on an individual basis.

In a pilot study investigating patients with inflammatory bowel disease [59], the substitution of factor XIII led to a decreased bleeding tendency, mitigated pain, and reduced stool frequency.

In severe chronic liver disease, factor XIII residual activities correlate with the degree of cirrhosis. Low levels of factor XIII (<50%) in patients during evaluation for liver transplantation is an unfavorable prognostic factor regarding future hemorrhagic episodes and survival [89]. Substitution with factor XIII should be considered if bleeding persists following second line substitution with FFP and/or PCC and if factor XIII levels continue to be markedly lower than the reference range (<50%) or if secondary bleeding occurs under the same circumstances.

A relevant factor XIII deficiency can develop in patients with leukemia and other hematological systemic disorders. On the one hand, elastase released from leukemia cells unspecifically destroys factor XIII [19]; on the other, factor XIII deficiency is induced by tumor-derived thrombocytopenia as in healthy individuals almost half of the circulating coagulation factor XIII is stored in platelets. In addition, leukemia can cause DIC with increased turnover and consumption of factors and inhibitors. Accordingly, proneness to bleeding in patients with leukemia depends on multiple parameters; the decision regarding substitution with factor XIII must be taken on an individual basis.

DIC can also result in relevant factor XIII deficiency. In the event of relevant hemorrhage the consumed factors should be substituted.

Indications and dosage: In severe congenital deficiency the substitution of factor XIII has become the most widely established practice. In the majority of cases no continuous substitution is required but rather a perioperative treatment on demand or in cases of bleeding [65].

Factor XIII shall be substituted in congenital factor XIII deficiency in order to treat resulting hemorrhagic diatheses such as bleeding and impaired wound healing and/or prophylactically, e.g. prior to surgery.	**1 C+**

[*] See section 0.4.

In principle, dosage of factor XIII in congenital deficiency follows the same rules as that of factor VIII and IX concentrates:

– 1 U/kg body weight of factor XIII leads to an increase in plasma activity by 1–2%.

In cases of severe hemorrhage 10–20 U/kg body weight per day should be administered until hemostasis is achieved. Prior to surgery up to 35 U/kg body weight or more are required until the desired levels are achieved. In major surgery standard levels (>50%) should be aimed for.

In continuous prophylactic administration significantly fewer repeated injections are required than in deficiencies of other factors due to the long biological half-life (100–120 h). In single cases the half-life of factor XIII may also vary considerably.

Factor XIII substitution for treating hemorrhagic diatheses should be performed if the latter are entirely or in part derived from an acquired factor XIII deficiency.	**2 A**
Factor XIII substitution can be performed as supportive therapy in impaired wound healing, e.g. following extensive surgery and injury, if these are entirely or in part derived from an acquired factor XIII deficiency.	**2 B**

The following rules apply in determining the dosage of factor XIII in acquired deficiency:

– In cases of bleeding at least 15–20 U/kg body weight per day until normal levels of factor XIII or hemostasis are achieved.
– In patients with therapy-refractory wound healing disorders 15–20 U each/kg body weight should be administered per day over the course of 3 days (days 0, 1 and 3).

Concluding assessment of factor XIII diagnostics:

– Factor XIII levels are not determined by the screening tests PT and activated PTT; if factor XIII deficiency is suspected factor XIII should always be determined separately.
– In case a prompt determination of factor XIII is not possible, the risk of persistent bleeding should be weighed against that of a blind administration of factor XIII, particularly in acute severe hemorrhage.

7.5.6 Absolute and Relative Contraindications

Known intolerance of the components in the product. In case of fresh thrombosis caution is advised due to the fibrin stabilizing effect. In long-term administration patients should be monitored carefully for the development of inhibitors.

7.6 Fibrin Glue

7.6.1 Preparation, Quality Criteria

The starting material is derived from pooled human plasma. The production is performed according to the Cohn/Oncley procedure.

7.6.2 Active Constituents

Active constituents of fibrin sealant are human fibrinogen, human thrombin, human factor XIII, bovine aprotinin and calcium chloride [20].

*7.6.3 Storage, Shelf Life and Package Sizes**

Factor concentrates should be stored at 2–8 °C, and fibrin glue in a deep-frozen state, when required. Information regarding the shelf life can be obtained from the package leaflet. Ready-to-use solutions should be administered immediately.

Fibrin sealants are available in a lyophilized and deep-frozen state.

– Dry substances in the combi set: 0.5 ml / 1.0 ml / 3.0 ml
– 2 deep-frozen solutions: 0.5 ml / 1.0 ml / 2.0 ml
– Dry substances in the kit: 1.0 ml / 2.0 ml / 5.0 ml,

7.6.4 Range of Application and Dosage

Fibrin glue has a wide application range in surgery. The immediate hemostatic effect of the sealant is taken advantage of. Sealing by fibrin analogously leads to the final stage of hemostasis, to polymerization of the fibrin monomer, by the addition of the thrombin solution and calcium chloride. The fibrinolysis inhibitor aprotinin is added to the sealant for stabilization of this fibrin lattice. The fibrin lattice resulting from the sealing process is completely metabolized. The use of fibrin sealant in patients with coagulopathy can lead to a reduction in the demand for factor concentrates.

Fibrin sealant is used in surgery to achieve local hemostasis in large bleeding parenchyma areas and by injection surrounding the area of bleeding gastrointestinal ulcers. It is also used for the fixation of transplants and implants (e.g. hernia mesh patches), for joining and fixation of nerve ends, sealing vascular prostheses, in septoplasty, sealing cerebrospinal fluid leaks etc. [44, 73, 84]. These applications are based on retrospective studies.

* See section 0.4.

Local application of fibrin sealant could be performed in patients requiring hemostasis in large bleeding parenchyma areas.	**2 C**
Further local applications of fibrin sealant could be as follows: to halt bleeding arising from gastrointestinal ulcers, fix transplants and implants (e.g. hernia mesh patches), join and fixate nerve ends, seal vascular prostheses, in septoplasty and to seal cerebrospinal fluid leaks.	**2 C**

Biochemical investigations demonstrate distinctive differences in comparison to autologous products [14].

7.6.5 Adverse Reactions

Local application of fibrin glue in neurosurgery has reportedly had a proconvulsive effect attributed to tranexamic acid that is possibly contained in fibrin sealant and has an effect on cerebral GABA receptors [25].

7.7 Documentation

According to article 14 German Transfusion Act (Transfusionsgesetz; TFG), there is an obligation to perform a patient- as well as product-related batch documentation for fibrinogen, PCC, factor VII and factor XIII concentrates, fibrin sealant and recombinant factor VIIa.

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