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6.1 Preparation

Human factor concentrates are prepared from large plasma pools. In addition, recombinant (genetically produced) human factor VIII and factor IX concentrates are commercially available [8, 36, 56].

6.1.1 Factor VIII Concentrates, Factor VIII/von Willebrand Factor Concentrates

Plasma-derived factor VIII as well as factor VIII/von Willebrand factor (vWF) concentrates are prepared from cryoprecipitates and contain vWF and moderately enriched factor VIII. Additional isolation steps include either immunoaffinity chromatography, ion exchange chromatography or precipitation procedures [1, 10, 26, 44]. Precipitation as well as chromatography lead to enrichment with functional vWF [12, 43].

6.1.2 Factor IX Concentrates

Plasma-derived factor IX concentrates are prepared from the supernatant of cryoprecipitates and from prothrombin complex concentrates (PCC) prepared from the supernatant. Factor IX is isolated by affinity chromatography or by ion exchange chromatography. The most recent generation of factor IX concentrates contains almost exclusively factor IX in highly purified form and has largely lost its former thrombogenicity [15, 68].

6.1.3 Recombinant Factor Concentrates

Recombinant factor concentrates are prepared in animal cell cultures using biotechnological procedures. Cells containing the genetic material of the protein in question release the factor which is subsequently isolated. Various products are available which differ by their manufacturing process. Subsequent processing and purification steps require in some cases the addition of plasma proteins (e.g. albumin as stabilizers). In third-generation products the addition of plasma proteins is abandoned during the entire manufacturing process. Factor VIII preparations available contain the natural factor VIII molecule at full length, while one preparation consists of a truncated factor VIII molecule lacking the B domain. A recombinant factor IX preparation is also available.

6.1.4 Activated Prothrombin Complex Concentrates

Activated prothrombin complex concentrates derived from plasma are produced from the supernatant of cryoprecipitates. Subsequent to isolation of the factors of the prothrombin complex the controlled activation of the factors II, VII, IX and X is generated as well as the standardization of the factor VIII inhibitor bypassing activity (FEIBA) [8, 33, 58].

6.1.5 Quality Criteria

The quality of a given hemostatically effective factor concentrate [24, 26, 31, 35, 43, 49, 60] depends on the starting material, the isolation or production processes, the clotting activity, the degree of purity of the concentrate (specific activity, additional protein contamination), the virus inactivation procedure, its immunogenicity, and the type of stabilizers employed.

6.2 Active Constituents

6.2.1 Factor VIII Concentrates

Factor VIII concentrates contain high concentrations of highly purified clotting factor VIII (factor VIII:C, i.e. factor VIII clotting activity) [10, 33, 43].

6.2.2 Factor VIII/von Willebrand Factor Concentrates

These concentrates contain factor VIII as well as hemostatically effective vWF, especially its highly polymerized multimers [12, 25].

6.2.3 Factor IX Concentrates

Factor IX concentrates contain high concentrations of factor IX [15, 61].

6.2.4 Activated Prothrombin Complex Concentrates

Activated prothrombin complex concentrates contain standardized FEIBA consisting of activated and non-activated clotting factors of the prothrombin complex [8].

6.2.5 Further Components

Depending on the particular product, factor concentrates derived from plasma may contain additional plasma proteins in varying concentrations, mainly albumin added as stabilizer, and, in albeit small amounts, fibrinogen, fibronectin, IgG and IgA immunoglobulins [10, 11]. Novel preparations have abandoned the addition of albumin. vWF can also serve as a stabilizer for factor VIII; some preparations contain small
amounts of heparin. The degree of purity of a given factor concentrate is stated as specific activity in units of the active constituent/mg total protein. The specific activity of presently available factor VIII concentrates ranges from 10–100 U factor VIII/mg protein, that of preparations without albumin as stabilizer can exceed 2,000 U/mg. The stabilized specific activity of factor IX concentrates exceeds 200 U/mg [15]. Some factor IX concentrates additionally contain antithrombin and/or heparin.

Some recombinant ‘first-generation’ factor concentrates contain human albumin added as stabilizer. In preparations presently available sugar molecules (e.g. saccharose or trehalose/mannitol) are added as stabilizer.

6.3 Physiological Function and Deficiency Diseases

6.3.1 Factor VIII

Factor VIII is an acute-phase protein formed mainly in the liver. It is the cofactor of the serine protease factor IXa, which activates factor X to Xa in the intrinsic coagulation system. Factor VIII is activated by thrombin and is inactivated by activated protein C. Factor VIII activity is reduced in the plasma of patients with hemophilia A. Their proneness to bleed correlates with the degree of factor VIII reduction. The mode of inheritance is X-linked recessive, its prevalence is 1 in 5,000 male births.

Hemophilia A is divided into three degrees of severity:

- Severe hemophilia A with residual factor VIII activity of ≤1% shows a marked bleeding tendency. These patients have a disposition for spontaneous bleeding, especially in knee, elbow and ankle joints. Repeated bleeding in the same joint causes reactive chronic synovitis, in turn causing increased bleeding tendency and finally, destruction of the joint (hemophilic arthropathy) [3, 44].
- Moderate hemophilia A is defined by a residual activity of >1 to ≤5%. Bleeding tendency is less severe; in residual activity of >2% joint bleeding occurs only rarely.
- Mild hemophilia A has a residual factor VIII activity of >5 to ≤15%, subhemophilia A of 15-50%. In the latter case bleeding often occurs only after severe injury or during surgery.

In patients with hemophilia A, the application of alloantibodies to factor VIII commonly called factor VIII inhibitors (hemophilia with inhibitors, mean incidence 25%) [2, 29, 48]. A very rare event is the development of spontaneously acquired factor VIII inhibitors caused by autoantibodies in persons with normal clotting factor concentrations [32]. The biological half-life of factor VIII is about 8–12 h. Increased requirement for factor VIII or shortened half-life occurs in patients with fresh large wounds, increased factor loss due to persistent bleeding, infections, hyperthyroidism as well as in infants and small children [44].

Pharmacokinetics and clinical effectiveness of recombinant factor VIII preparations do not differ essentially from those of factor VIII preparations from human plasma.

6.3.2 Von Willebrand Factor

The vWF is a high molecular, adhesive glycoprotein with a multimeric structure (molecular weight 500–20,000 kDa). It is formed in endothelial cells and alpha granules of platelets and fulfills several functions [12, 46, 52]:

- In primary hemostasis, it connects platelets with collagen of the subendothelial layer of the blood vessel [25]. vWF activity can thus be measured as collagen-binding activity.
- It participates in platelet aggregation by adhesion to platelet membrane receptors. This platelet aggregation can be activated in vitro by the antibiotic ristocetin. For this reason the vWF is known as the ristocetin cofactor and is measured by adding ristocetin to platelet-rich plasma.
- vWF forms a complex with factor VIII, thereby extending the half-life of factor VIII in plasma. In the absence of vWF the half-life of factor VIII in plasma is drastically reduced.

The biological half-life of vWF is 6–12 h; infusion, subcutaneous injection, or nasal application of the vasopressin analogue DDAVP (1-desamino-8-D-arginin-vasopressin; desmopressin) releases vWF and factor VIII from the body’s reservoirs and causes an approximately three-fold increase over initial plasma levels. Thus DDAVP can be employed to stop bleeding in mild forms of von Willebrand syndrome (type 1) and in mild hemophilia A during minor bleeding episodes or minor surgery [12, 38].

Three types of von Willebrand syndrome can be distinguished [53]:

- In type 1 the concentration of vWF, its activity and factor VIII are all reduced to 50–10%.
- In type 2 the plasma concentration of von Willebrand molecules is normal or slightly reduced but their function is characteristically impaired. There are several subtypes of type 2. Type 2a, in which large and intermediate molecular multimers are lacking, is most frequent. Type 2b is characterized by increased binding of the vWF to the glycoprotein complex Ib of platelets and therefore may go along with thrombocytopenia. Administration of DDAVP may aggravate this condition. Therefore, it is required to closely monitor platelet count. The rare type 2M is characterized by a reduced platelet-dependent function with normal distribution of multimers and aberrant triplet pattern. In the type 2N which is also rare the binding capacity of vWF to factor VIII is disturbed, thus imitating a mild form of hemophilia A in diagnostic tests [59]. Type 2N requires treatment with factor VIII/vWF concentrate.
In type 3 vWF is lacking while factor VIII:C is markedly reduced to but a few percent of its normal concentration. Congenital type 1 von Willebrand syndrome is the most common bleeding disorder (vWF concentrations between 25 and 50%, mild form, prevalence in general population 1:100). Type 3 has a prevalence of 1:100,000 [52]. Acquired von Willebrand syndrome has been observed with the use of certain medications (e.g. valproic acid), in lymphoproliferative diseases, less often in myeloproliferative diseases, in monoclonal gammopathies, in hypothyroidism and in certain cardiac defects [46].

6.3.3 Factor IX

Factor IX is the proenzyme of the serine protease factor IXa which activates factor X in the presence of cofactor VIII. Factor IX is formed in liver cells. It is part of the prothrombin complex and thus requires vitamin K for synthesis. Factor IX formation is encoded by a gene on the X chromosome. The half-life of factor IX is 20–24 h. Factor IX activity is reduced in hemophilia B; the bleeding tendency correlates with the degree of diminished factor IX activity. The classification in degrees of severity corresponds to that of hemophilia A [58]. The prevalence of hemophilia B is 1:30,000 male births. The prevalence of factor IX inhibitors is about 0.5% in hemophilia B.

Recovery of the recombinant factor IX seems to amount to about 40–50% below that of natural plasma factor. The half-lives are identical [27, 54].

6.3.4 Activated Prothrombin Complex

Activated PCC (FEIBA) does not occur in vivo. Its impact on hemostasis can be deduced from reduced coagulation times as evidenced by group tests such as aPTT or shortened r-time in thrombelastogram. There is, however, no clear-cut correlation between laboratory results and clinical effectiveness [8, 33].

6.3.5 Recombinant Activated Factor VII

See chapter 7.

6.4 Storage, Shelf Life and Package Sizes*

6.4.1 Storage

Generally, factor concentrates must be stored protected from light. The standard storage temperature for concentrates is 2–8 °C. Some factor concentrates can be stored temporarily or over its entire shelf life at up to 25–30 °C. For some concentrates it was documented that the factors were stable for up to 12 h after preparing the solution. However, from a microbiological perspective, the ready-to-use solution should be used immediately after preparation. The particular instructions for use/expert information are referred to.

6.4.2 Package Sizes

The following package sizes are usual:

**Factor VIII:**
- 250/500/1000/1,500/2,000 U/package.

**Factor VIII/vWF:**
- 450/900 and 500/1000 U/package.

**Factor IX:**
- 200/600/1,200 U/package and
- 250/500/1,000 U/package and
- 300/600/1,200 U/package and
- 500/1,000 U/package.

**Activated PCC (FEIBA):**
- 500/1000 U/package.

6.5 Range of Application, Dosage, Mode of Administration*

6.5.1 General Information

Appropriate clotting factor concentrates are used to treat hemophilia A or B or von Willebrand syndrome. The following recommendations are based on consensus reports [14, 37, 61–63] and on review articles on the treatment of hemophilia [7, 17, 26, 47, 58, 63].

Criteria determining indications and dosage are:

- The principal goals of hemophilia therapy, namely:
  - prevention of bleeding,
  - treatment of bleeding, its complications and sequelae,
  - maintaining and/or restoring joint functions,
  - integrating hemophiliacs into a normal social life.
- Further criteria influencing hemophilia therapy:
  1. patient groups
     - age (e.g. small children and infants require higher doses/kg body weight because of higher relative plasma volume),
     - medical history,
     - degree of severity,
     - inhibitor formation,
     - individual variations in recovery and half-life,
     - adverse reactions of therapy;
  2. clinical situation
     - frequency and site of bleeding,
     - state of the particular joints,
• accompanying diseases (hepatic diseases, especially HCV and HBV; HIV),
• other individual indications for treatment;
3. social situation, the patients' wishes as well as the physician's experience.
Dosage recommendations listed below with indications and contraindications are average initial doses which should be adapted to individual needs considering the goals and criteria indicated.

On principle treatment shall be carried out at a hemophilia center (so-called Comprehensive Care Center) or in close cooperation with such an institution [62, 63, 66].

The German Federal Joint Committee has enacted a guide for out-patient treatment of hemophilia patients in hospitals in accordance with article 116b SGB V (German Code of Social Law, Book V) specifying diagnostic and therapeutic procedures to be offered as well as requirements of the hemophilia center regarding personnel and equipment (Bundesanzeiger no. 73 p. 4003 dated April 18, 2007, see also www.g-ba.de).

6.5.2 Indications for Replacement Therapy Using Factor Concentrates

Treatment principles:

Factor replacement on demand shall be performed during spontaneous or traumatic bleeding episodes at any bleeding site if the bleeding exceeds a minimum degree (e.g. minor skin bleeding) [40, 57].

Full-time prophylactic replacement therapy shall be carried out mostly in children and adolescents with severe hemophilia in the form of physician-controlled self-administered treatment with the main intention of preventing hemophilic arthropathy [23, 30, 41, 51, 67, 69].

Full-time prophylactic replacement therapy can be carried out individually in adults with the intention of preventing the development of arthropathies as a late consequence [3, 18, 23, 50].

Prophylactic therapy to prevent bleeding shall be provided before and after surgical interventions.

Temporary prophylactic therapy to prevent bleeding should be provided during periods of major physical or psychic stress (e.g. rehabilitation, exams) [61, 63].

– Factor VIII concentrates are administered in hemophilia A when factor VIII activity is reduced or in patients who have developed factor VIII inhibitors.
– Factor VIII/vWf concentrates are administered according to their licensed use in cases of vWf deficiencies, i.e. in congenital or acquired von Willebrand syndrome, factor VIII deficiency and acquired factor VIII inhibitors.
– Factor IX concentrates are given in hemophilia B (factor IX deficiency).
– Activated PCC and recombinant factor VIIa preparations are predominantly used for treating patients with factor VIII inhibitors [8].
– Replacement therapy can be supported by local measures (e.g. mechanical pressure, application of antifibrinolytic drugs, fibrin glue).

6.5.3 Dosage, Mode of Administration

Several reviews on dosage of replacement therapy in hemophilia A and B as well as in von Willebrand syndrome have been published in recent years [17, 26, 33, 43, 44, 61, 63], but hardly any dose-finding studies were published. Recommended doses are essentially based on the Consensus Paper on Hemophilia Treatment in Germany, updated in 1999 [63].

The activity of clotting factors is expressed in units. One unit of a clotting factor corresponds to '100% factor activity' and is defined as the activity in 1 ml of pooled plasma from healthy donors.

1 U/kg body weight increases the respective plasma factor concentration by 1–2%.

The specifications regarding ‘incremental recovery’ are referred to in the expert information provided by the manufacturer.

Frequently patients with severe hemophilia A or B will show an increase of only 1% after the first injection. After a dose of 1 U/kg body weight an increase of about 2% can only be expected after an equilibrium between blood and extravascular compartments has been achieved, thereafter the dose may be reduced as appropriate.

Patients with severe or moderate hemophilia A usually require exclusively factor VIII concentrates. In contrast, most patients with mild hemophilia A or von Willebrand syndrome type 1 can be treated with DDAVP, with the exception of severe bleedings or during major surgery. Prior to administration of DDAVP the rate of biologic response should be tested [22, 38, 54, 59].

– Clotting factor concentrates are usually administered slowly as bolus i.v. injection.
– Because of the stability of currently available factor concentrates, constant plasma levels can be achieved in many clinical situations by continuous infusion. By this the total...
dose can be reduced without sacrificing effectiveness. However, in particular the potentially increased development of inhibitors against the administered factor during continuous infusion is discussed [9].

- The recommended doses represent a range of standard initial doses. Further dosage should be adjusted according to the clinical situation. Calculations for dosage are based on the half-life of the clotting factor and should be monitored by measuring the recovery of the replaced factor in patients’ plasma. Numerous bleeding episodes (e.g. bleeding into joints, epistaxis) may be successfully treated with 1–2 injections, if given promptly and in sufficient dose.

6.5.3.1 Replacement in Children with Hemophilia A, B or von Willebrand Syndrome

Full-time prophylactic replacement therapy to achieve the goals stated under 6.5.1 [33, 58]:

- As a general rule, this treatment is recommended for children with severe hemophilia [62, 71].
- Treatment is to be initiated without delay after the first episode of bleeding into joints or after other frequent bleedings.
- Treatment must be individually adjusted according to the clinical situation and age.

Mean dose: 20–30 U/kg body weight at least 3 times per week.
Because of the longer half-life of factor IX, fewer injections/week suffice in hemophilia B [23, 30, 41, 51, 58, 62, 67, 69].

Exclusively referring to clinical trials investigating full-time prophylactic replacement therapy in children with hemophilia, the general international consensus is to give a 1 A recommendation [41, 62]. However, the exact dose of factor infusion, starting time, and duration of therapy are still under discussion.

**Factor replacement on demand in children:**
- individual dose adjustment according to clinical situation
- duration: until cessation of bleeding
- Reduction of total dose is possible by means of continuous infusion without loss of effectiveness (table 6.1).

As a rule, moderate hemophilia is treated on demand (doses corresponding to those applied in severe hemophilia). Continuous replacement therapy in moderate hemophilia depends on the frequency of bleeding and on the particular clinical situation and is performed similar to treatment of severe hemophilia.

With the exception of severe bleeding or major surgery, most patients with mild hemophilia or von Willebrand syndrome type 1 can be treated with the synthetic vasopressin analogue DDAVP (desmopressin) at a dose of 0.3 µg/kg body weight or as nasal spray (dosage see expert information) [38]. Because of the danger of hyponatremia and cerebral seizures, DDAVP is not indicated in children under the age of 4 years.

Life-threatening bleeding in patients with type 1, 2 or 3 von Willebrand syndrome is treated with factor VIII/vWf concentrates. Dose and duration of treatment depend on the particular clinical situation.

Furthermore, prior to surgery with risk of bleeding, patients with type 1, 2 or 3 von Willebrand Syndrome should be substituted with factor VIII/vWf concentrates. Dose and duration of the therapy depend on the clinical situation [4, 20, 21, 42, 45].

**Table 6.1. Treatment on demand in childhood: mean initial dose**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Mean initial dose U/kg body weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding into joints and muscles</td>
<td>30–40</td>
</tr>
<tr>
<td>Life-threatening bleeding</td>
<td>80–100</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>Major wounds, e.g. tonsillectomy</td>
<td>80–100</td>
</tr>
<tr>
<td>Minor wounds</td>
<td>50–100</td>
</tr>
</tbody>
</table>

6.5.3.2 Replacement in Adults with Hemophilia A, B or von Willebrand Syndrome

As a rule, moderate hemophilia is treated on demand. Indication for full-time replacement therapy depends on the frequency of bleeding and the particular clinical situation. Procedure and dosage are similar to those in severe hemophilia.

With the exception of severe bleeding or major surgery, most patients with mild hemophilia or von Willebrand syndrome type 1 should be treated with the synthetic vasopressin analogue DDAVP (desmopressin) at a dose of 0.3 µg/kg body weight or as nasal spray (dosage see expert information) [38].

Life-threatening bleeding in patients with type 1, 2 or 3 von Willebrand syndrome should be treated with factor VIII/vWf concentrates. Dose and duration of treatment depend on the particular clinical situation.

Furthermore, prior to surgery with risk of bleeding, patients with severe type 1 von Willebrand Syndrome or with type 2 or 3 von Willebrand Syndrome should also be substituted with factor VIII/vWf concentrates. Dose and duration of the therapy depend on the individual clinical situation [20, 21, 42, 45].
Recommended doses for treatment on demand are: (dose-finding studies have not been published in sufficient number [57]. Recommended doses are essentially based on the Consensus Paper on Hemophilia Treatment in Germany, updated in 1999 [63]) (table 6.2).

Continuous prophylactic factor replacement therapy can be carried out [3, 17, 18, 23, 50, 61, 63]:
- in patients with recurrent bleeding with the danger of irreversible damage,
- individually to prevent the development of arthropathies as a late consequence,
- under extreme physical or psychological/mental stress,
- during rehabilitation.
Mean dose: 20–30 U/kg body weight at least 3× weekly
Because of the longer half-life of factor IX, fewer injections/week suffice in hemophilia B [58]. Individual adjustment and maintenance therapy required according to the clinical situation.
Duration: until a symptom-free interval of several weeks is attained, or at least until cessation of symptoms.
Continuous infusion over several days may result in a reduction of the total dose without loss of effectiveness.

### Table 6.2. Treatment on demand in adults: mean initial dose

<table>
<thead>
<tr>
<th>Indication/type of bleeding</th>
<th>Mean initial dose (U/kg body weight)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding into joints and muscles</td>
<td>20–40</td>
</tr>
<tr>
<td>Life-threatening bleeding</td>
<td>50–80</td>
</tr>
<tr>
<td>Bleeding into soft tissue</td>
<td></td>
</tr>
<tr>
<td>- Severe or extensive bleeding (e.g. cerebral hemorrhage, tongue bite, carpal tunnel syndrome, retroperitoneal bleeding, femoral, calve, muscle hemorrhage)</td>
<td>40–60</td>
</tr>
<tr>
<td>- Minor bleeding into skin and muscles</td>
<td>15–30</td>
</tr>
<tr>
<td>Mucosal bleeding, urogenital bleeding</td>
<td></td>
</tr>
<tr>
<td>- Gastrointestinal bleeding and bleeding of the oral cavity</td>
<td>30–60</td>
</tr>
<tr>
<td>- Epistaxis</td>
<td>20–40</td>
</tr>
<tr>
<td>- Hematuria</td>
<td>20–40</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>- Major wounds and/or high tendency of bleeding, including tonsillectomy</td>
<td>50–80</td>
</tr>
<tr>
<td>- Minor wounds (tooth extraction, herniotomia)</td>
<td>25–40</td>
</tr>
</tbody>
</table>

*Exploratory range.

### 6.5.3.3 Indications and Recommended Doses for Treating Patients with Factor VIII Inhibitors in Hemophilia A

**General remarks:** The recommendations in this section are derived from the following publications [8, 16, 61, 63].

**Treatment of acute bleedings (children and adults):**

- Low Responders (≤5 Bethesda units, BU, or the possibility of overriding acute bleedings with factor VIII concentrates):

  a) High-dose factor VIII infusions shall be administered up to hemostatically effective factor VIII levels [5, 28].

  b) Activated PCC (FEIBA) shall be given as initial dose: up to 100 U/kg body weight and a maintenance dose of up to 100 U/kg body weight twice daily [6, 19, 28, 65].

  c) Alternatively recombinant factor VIIa shall be given, mean initial dose 90 μg/kg body weight or 270 μg/kg body weight as single dose (see section 7.4) [6, 28].

- High Responders (>5 BU):

  a) Activated PCC (FEIBA) shall be given as initial dose: up to 100 U/kg body weight and a maintenance dose of up to 100 U/kg body weight twice daily [6, 19, 28, 65].
b) Alternatively recombinant factor VIIa shall be given, mean initial dose 90 μg/kg body weight or 270 μg/kg body weight as single dose (see section 7.4) [6, 28, 34, 39, 55, 64, 70].

c) In emergencies and failure of a) and b) immunoadsorption apheresis should be considered [13].

**Inhibitor elimination by inducing immune tolerance:**

- **Children:**
  - **Low Responders (<5 BU):**
    Even if no clinical symptoms occur factor VIII concentrate could be given 3 times per week at a dose of 50–100 U/kg body weight, until normal recovery and half-life are achieved. Monitoring for inhibitors necessary once or twice per week, followed by continuous therapy [5, 28].
  
  - **High Responders (>5 BU):**
    Factor VIII concentrate at a dose of 100–200 U/kg body weight shall be given twice daily up to normalization of recovery and half-life over several months, followed by individually adjusted continuous therapy. Combination with FEIBA at a dose of up to 50 U/kg body weight twice daily during inhibitor elimination may be used to reduce the bleeding tendency [5, 6, 28].

  In case of unsuccessful inhibitor elimination, this therapy mode should be discontinued generally after 1 year.

Alternatively, recombinant factor VIIa can be given (initial dose 90 μg/kg body weight or 270 μg/kg body weight as single dose) to treat bleeding tendency during inhibitor elimination.

- **Adults:**
  - **Low Responders (<5 BU):**
    As a rule, elimination therapy is not recommended during continuous therapy with factor VIII concentrate, 50 U/kg body weight three times per week [5, 28].

  - **High Responders (>5 BU):**
    Factor VIII concentrate, dose: 100–150 U/kg body weight should be given twice daily up to normalization of recovery and half-life over several months, followed by individually adjusted continuous therapy. Combination with FEIBA at a dose of up to 50 U/kg body weight twice daily during inhibitor elimination may be used to reduce the bleeding tendency [5, 6, 28].

  In case of unsuccessful inhibitor elimination, this therapy mode should be discontinued generally after 1 year.

Alternatively, recombinant factor VIIa can be given (initial dose 90 μg/kg body weight or 270 μg/kg body weight as single dose) to treat bleeding tendency during inhibitor elimination.

### 6.5.4 Absolute and Relative Contraindications

- Correct indications provided, there are no contraindications for factor VIII concentrates, factor VIII/vWF concentrates or factor IX concentrates.

- Activated PCC preparations (FEIBA), recombinant factor VIIa preparations: These preparations may aggravate disseminated intravascular coagulation. In patients with known or suspected coronary heart disease as well as in acute thromboembolic disorders, these preparations should be strictly reserved for cases with life-threatening bleedings.

### 6.6 Adverse Reactions

See chapter 11.

### 6.7 Documentation

The product type, batch number and recipient of factor VIII concentrates, factor VIII/vWF concentrates, factor IX concentrates and activated prothrombin concentrates must be documented in writing in accordance with section 14 of German Transfusion Act (Transfusionsgesetz; TFG).
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