Extended half-life (EHL) clotting factor concentrates

With the help of members of the Medical Advisory Board of the DHG
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History of Haemophilia Treatment

Up until the 1960’s, bleeding episodes in haemophilia were treated with whole blood or plasma. The proportion of clotting factor present in whole blood or plasma was so low that there was very little effect for bleeding episodes. Prior to the development of viral inactivation procedures in the mid-1980s, people with haemophilia who had previously received large pool plasma-derived factor concentrates were infected with the hepatitis C virus (HCV). A considerable number of these patients were also infected with human immunodeficiency virus (HIV).

Today’s optimum therapy is prophylaxis with clotting factor concentrates, in which it is attempted to prevent bleeding by regular intravenous infusion of the plasmatic or recombinant clotting factor which is deficient (with haemophilia A factor VIII and with haemophilia B factor IX). This greatly reduces bleeding and allows the patient to live a relatively normal life.

Factor VIII (haemophilia A) and factor IX (haemophilia B) can be manufactured as recombinant proteins using a cell line. Since the beginning of the 1990’s recombinant factor concentrates have been available in order to avoid contamination with viruses. Currently, some recombinant products with an extended half-life are available, which can increase the protection and/or reduce the number of infusions. There are also new and exciting therapies being developed that will allow subcutaneous administration, much extended dosing intervals and in the long run, the cure for both haemophilia A and B, as the ongoing gene therapy trials progress.

This brochure is aimed to provide an overview of these developments with a focus on products with extended half-life, currently available or soon to be available.

WFH Timeline. http://www1.wa.org/2/1/1_1_3_Link1_Timeline.htm attached on 1st November 2015.

Individual Dosing

Factor levels, bleeding and arthropathy

Haemophilia is a chronic lifelong disease, which can lead to pain, joint damage or life-threatening bleeding if the treatment is insufficient. Joint damage can lead to a considerable reduction in the quality of life. The prevention of joint damage is an important treatment goal. The main goal of treatment is to enable patients to live a normal life. While treatment has been significantly improved in the last 30 years, people with haemophilia are still faced with difficulties due to their condition as demonstrated in longitudinal studies with follow-ups as long as 30 years. Despite seemingly optimal prophylactic therapy, patients reported marked joint damage in early to middle age. After 10 years patients reported changes in ankle joints, after 15 years patients reported changes in knee joints and after 20 years patients reported changes in elbow joints, all of which were clinically confirmed. Despite low bleeding rates, a trough level (ie a factor level directly before the next injection) of 1% appears to be insufficient. Trough levels of 3%, 5% or even 10% are being discussed; however, some patients with a trough level of 3% may continue to experience bleeding episodes whereas a patient with a trough level maintained at 1% may not bleed at all. This emphasizes the importance of tailored individual treatment for patients.

Extended half-life products allow not only less frequent infusions, but also higher troughs than standard half-life products when used at the same frequency and dosing. Thus, these products may help manage patients who do well with a trough level of 1% as well as those who need higher troughs to prevent all bleeds. A long-term effect on the joints will, of course, only occur after a similar long observation period as in the study described above.

Half-life extension and alternative technologies

There are several new treatment pathways and technologies that will become available to patients with haemophilia A and B in the coming years. These technologies may seem complex, but we can divide them easily as follows:

- **PEGylation:** chemical modification of FVIII and FIX molecules by attachment of PEG. PEGs (polyethylene glycols) are chemical substances that the body cannot degrade, but may shed via different routes. The rate of excretion via the kidney depends on the size of the PEG molecule and is not yet fully understood.

- **Protein fusion:** genetic engineering to produce factor VIII or factor IX in the form of a large protein that consists of a coagulation factor linked with another protein. The fusion partner protein may be full-length or part of an endogenous protein (albumin or immunoglobulin fragment, respectively). These fusion proteins can be completely degraded and recycled by the body. Some of these products are produced in a human cell line so that they are extremely similar to the body’s proteins.

- **Modification of clotting factor amino acid sequence:** genetic engineering to change the primary structure of a clotting factor. This approach was used to obtain the single-chain FVIII. In the body, factor VIII is cleaved before release into the bloodstream. The products of this cleavage, called FVIII light and heavy chain, circulate together as a protein complex. Introduction of changes at specific sites of the FVIII protein through genetic engineering prevents the cleavage and extends the FVIII half-life.

In most cases in haemophilia A the injection interval can be prolonged from three times per week to twice per week or from every two to every three days. In Haemophilia B the dosing frequency can be reduced from twice per week to once per week. Some patients may be able to extend their infusions to every 10-14 days. In many cases a much better protection of the patient is also achieved. In the medium term further advances in treatment for haemophilia A (including patients with inhibitors) will be available such as an antibody that will be administered subcuaneously (under the skin). In the long term, gene therapy will also be available.

### In short-term or already available

- **Chemical modification**
  - PEGylation

- **Protein fusion**
  - FVIII or IX + Fc region of immunoglobulin G\(^3\)
  - FVIII or IX + albumin\(^4\)

- **Protein sequence modification**
  - Single-chain FVIII molecule\(^5\)

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**PEG = polyethylene glycol**

Medium to long term possible therapies

There are several therapies currently being investigated that aim to extend the half-life of clotting factors or otherwise achieve a prolonged therapeutic effect.

- **Antibodies**
  - Emicizumab (ACE910, factor VIII-mimetic antibody)¹
  - Concizumab (TFPI inhibitor)

- **Chemical modifications**
  - Polysialylation (conjugation with polysialic acid)²

- **Protein fusion**
  - XTENylation³

- **RNAi (gene silencing)**
  - Antithrombin III downregulation³

- **Gene therapy**
  - Viral vectors with a correct copy of FVIII or FIX gene

FVIII-mimetic antibody: a monoclonal bispecific antibody that binds FⅨa and FX. Normally, FⅨa activates FX, but requires FVIII to do so. Emicizumab mimics that function of FVIII.

Polysialic acid: a biocompatible and biodegradable natural sugar polymer.

XTENylation: XTEN is a large, unstructured recombinant protein consisting of 864 natural amino acids, which when merged to a peptide or protein, prolongs its half-life in the plasma.


The following are major methods for the half-life extension as well as non-replacement therapies under development:

- **Chemical modification**
  - PEG sialylation

- **Protein fusion**
  - Fc albumin
  - XTEN

- **Sequence modification**
  - Single-chain FVIII

- **Antibodies**
  - Emicizumab
  - Concizumab

- **RNAi (gene silencing)**
  - AT

- **Gene therapy**
  - Viral vectors encoding FVIII or FIX

XTEN = polypeptide composed of natural amino acids
PEG = polyethylene glycol
TFPI = tissue plasminogen factor pathway inhibitor
AT = antithrombin
The mechanism of half-life extension by PEGylation

The illustration shows how PEGylation extends the clotting factors’ half-life. The polymer (PEG), represented as a green chain molecule, shields the protein from degrading substances and slows down its clearance.

PEGylation of proteins (clotting factors)

► Chemical attachment of PEG molecules of different sizes to specific sites on the protein via covalent bonds

► Site-specific and controlled

► Site-specific

• rFVIII (BAY94-9027) – 60 kDa PEG
• rFVIII (N8-GP) – 40 kDa PEG
• rFIX (N9-GP) – 40 kDa PEG
• rFVII (N7-GP9) – 40 kDa PEG

► controlled

• rFVIII (BAX855) – 20 kDa PEG

The individual manufacturers use differently sized PEG molecules and bind these at different sites of the clotting factor.

kDa = kilodalton = size of the PEG molecule
BAY = Bayer
N = Novo Nordisk
BAX = Baxalta / Shire
GP = glycopegulation
Site-specific = binding site is predetermined (all procedures), very specific structures are created, to which PEG binds
In Bax855, PEG binds to 1-2 lysines (therefore controlled)
Covalent bond = strong chemical bond
Site-specific, covalent attachment of a branched PEG molecule of 60 kDa total size (about 2 x 30 kDa)

**Site-specific PEGylation to prolong the FVIII half-life**

The illustration shows the key features of glycoPEGylation in the case of factor IX. PEG molecules are attached to N-glycans (complex carbohydrates linked to proteins) on the activation peptide (pink) within the clotting factor (light blue). This modification protects the factor from premature degradation. When bleeding ensues and the factor is needed to stop it, the activation peptide is cleaved off together with the PEG, which activates the clotting factor and allows it to promote clotting. FVIII differs in structure from FIX and so in the case of N8-GP PEG is attached to a different carbohydrate chain (called O-glycan), but FVIII activation proceeds in a similar way, with the protein fragment containing the PEGylated O-glycan being cleaved off.

**ACT-PEP = activation peptide**

Full-length PEGylated rFVIII (BAX855)

- BAX 855 is a PEGylated full-length (with the whole B domain retained, as opposed to B domain-deleted) recombinant FVIII.
- Covalent binding of 20 kDa PEG molecules
- Controlled PEGylation of exposed amino acid side-chains

The illustration shows the clotting factor (blue) and 4 polymers (green), which represent PEG. The PEG polymers slow down clearance of the clotting factor.


Polysialylation (conjugation with polysialic acid)

- Biocompatible and Biodegradable Natural Polymer
- Polysialic acid (PSA) could significantly improve half-life, although a clinical trial of factor VIII-PSA was discontinued due to disappointing results. Opportunities to use this technology with other clotting factors are being explored.

The illustration shows the clotting factor (blue) and 9 worm-shaped polymers (polysialic acid) (red). The red polymers protect the clotting factor from rapid degradation and slow down its renal clearance.

Polysialic acid is a complex carbohydrate produced and degraded by the body itself as part of glycoproteins and glycolipids.

The mechanism of action is similar to the PEGylation.

**XTENylation**

→ **XTENylation:**

- a clotting factor is modified by fusion with XTEN, a biocompatible and biodegradable, physiologically inert polypeptide

- XTEN could significantly improve half-life

**Protein fusion**

→ **Fusion of the clotting factor with another blood protein or a protein fragment (e.g., albumin and IgG-Fc, respectively), whose half-life is longer.**

In protein fusion technology, a recombinant clotting factor is fused with another protein (immunoglobulin fragment or albumin) by genetic engineering, resulting in a single fusion protein. Immunoglobulins and albumins show longer half-lives (weeks) than clotting factors (hours). The fusion prolongs the half-life of the clotting factor. These fusion proteins are completely degraded and recycled naturally by the body.

The illustration shows the clotting factor (blue) and 2 coil-shaped polymers (XTEN, amino acid sequence) (green). The green polymers delay clearance of the clotting factor.

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rFIX-FP
Factor IX-albumin fusion protein

- Albumin is a protein with a long half-life\(^1\), produced in large quantities in the body.
- Genetic fusion of recombinant albumin and rFIX with a cleavable linker\(^4\).
- Recycling by FcRn (neonatal Fc receptor)\(^3\).
- When activated, FIXa is released and albumin is split off\(^2\).

rIX-Albumin fusion\(^2\)
CSL-654, rIX-FP

The illustration shows the clotting factor IX (dark blue) fused with albumin (yellow). The activation peptide (connecting the two functional parts of the protein is shown in green). The arrows indicate cleavage sites (the cleavage activates FIX). The albumin protects the factor from rapid degradation. When bleeding starts and the clotting factor is needed at the site of blood vessel injury, the activation peptide is excised, the albumin molecule split off and the activated clotting factor promotes blood clotting.

rFIX-Fc and rFVIII-Fc fusion proteins

- rFIX-Fc and rFVIII-Fc each consist of a single FIX or FVIII molecule fused to two Fc domains of the human IgG1.\(^1,2,3\).
- Recycling by FcRn

A single FIX molecule (blue) or FVIII molecule (blue) is fused to a dimeric (double) Fc region of human IgG1 (green). FcRn (neonatal Fc receptor) reverses the uptake of FVIII-Fc or FIX-Fc and recycles it back to the bloodstream. Recycling by FcRn protects the clotting factor from degradation.

rFIX-Fc = recombinant factor IX-Fc fragment fusion protein
IgG = immunoglobulin G

Single-chain FVIII molecule ¹⁻⁵

- rFVIII with a truncated B-domain
- Covalently bound FVIII-HCh (heavy chain) and FVIII-LCh (light chain)
- Increased binding affinity to VWF
- Activation by thrombin generates native FVIIIa

Site-specific changes in the FVIII gene nucleotide sequence, and thus in its protein amino acid sequence, lead to formation of a stronger, covalent bond between the heavy (light blue) and light chain (dark blue) of the clotting factor, generating a single molecule, as opposed to two parts (heavy and light chain) of FVIII held together by weaker interactions in the unmodified FVIII. This also results in stronger binding to VWF, which protects FVIII from rapid degradation. Activation by thrombin produces a normal active clotting factor VIII.

Concept of a FVIIIa-mimetic bispecific antibody

The antibody imitates (mimics) the function of the activated factor VIII molecule, binding both factor IXa and factor X (bispecific).

- The bispecific antibody allows interaction between FIXa and FX, thereby activating FX and promoting blood clotting.

Monoclonal bispecific antibody binds FIXa and FX (lower panel), so that FIXa can activate FX. This is exactly what FVIII does (upper panel).


Gene silencing: Downregulation of antithrombin (AT)

Downregulation of antithrombin by RNAi

→ Antithrombin is a clotting inhibitor that is normally present in the body of healthy individuals, which prevents blood from clotting excessively.

→ RNA interference (RNAi) is a natural mechanism of gene silencing (to decrease synthesis of respective proteins) in many organisms.

The siRNA molecule (ALN-AT3) that downregulates antithrombin is conjugated with N-acetylgalactosamine (a type of sugar), which allows its uptake by the liver cells. Once in the liver cell, the siRNA molecule targets the mRNA encoding antithrombin, leading to its breakdown, so that no antithrombin can be synthesized.

dsRNA = double stranded; siRNA = small interfering RNA (ribonucleic acid); RISC = RNA-induced silencing complex; mRNA = messenger RNA; RNA = ribonucleic acid


ALN-AT3

Antithrombin (AT) inhibits thrombin, which hinders blood clotting.

→ AT depletion by ALN-AT3 boosts thrombin generation in severe haemophilia A individuals (FVIII <1%)

Increase in thrombin generation correlates well with AT depletion. Total AT depletion (blue curve) boosts thrombin generation to about 50% of normal (black curve).

Antibodies:
Blocking a clotting inhibitor (TFPI)

Blocking a clotting inhibitor (TFPI)

To prevent the blood clotting from turning into thrombosis, there are natural pathways of clotting inhibition, for example tissue factor pathway inhibitor (TFPI). In patients with haemophilia, the clotting process is already hindered, so blocking a clotting inhibitor rebalances the procoagulant and anticoagulant factors, which promotes normal blood clotting in people with haemophilia.

Blocking Tissue Factor Pathway Inhibitor (TFPI)

The FVIIa/TF complex activates FX to FXa. This process is inhibited by TFPI (tissue factor pathway inhibitor), so that less FXa is produced. Thus, inhibition of TFPI produces more FXa. FXa is also generated in another pathway, which involves FVIII and FIX.

Gene therapy

The essential components of gene therapy

Forcing the body’s cells to produce the missing protein

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<th>Vector</th>
<th>Production</th>
<th>Incorporation into the target organ</th>
<th>“Protein factory” in the body</th>
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<td>Therapeutic agent</td>
<td>Drug-Delivery-System</td>
<td>Gene-/Vector-copies</td>
<td>Gene-/Vector-Internalisation</td>
<td>“Protein Factory”</td>
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The desired gene sequence is first inserted into a vector (transport vehicle, often a nonpathogenic virus). The viral vector brings the DNA sequence into the target cell. There, it is deposited (episomally) separately from the patient’s DNA outside the chromosomes or integrated into the patient’s DNA (chromosomes). In both cases, the gene sequence can be read off by the cell’s machinery, leading to synthesis of the missing protein (protein factory).

Illustration modified according to UnicQure lecture “GeneTherapy for Haemophilia, is the Technology Ready for Prime Time?”, presented at the Hamburg Haemophilia Symposium, 7-8 November 2014.

Half-life extension

The following pages provide an overview of the extended half-life products already approved and products under development.

Notably, factor VIII products show half-lives extended 1.7 fold at best (1.5 fold on average). None of the different technologies presented in the previous chapter provide any major difference in the half-life extension.

This is in contrast to the extended half-life FIX products, each of which shows on average a 5-fold half-life extension.

Since individual rFVIII and the rFIX products differ in terms of patient populations they were tested on and the study design, it would be inaccurate to make side-by-side comparisons of the products described here. The production cell line (animal or human) or the technology of modification (e.g. chemical or by genetic engineering) of individual products may all prove to have unique and specific advantages in different patients.

On the other hand, despite encouraging initial results of non-replacement therapies and gene therapy, large phase III studies are yet to be completed.

Therefore, at the end of this chapter, the advantages and disadvantages of the initially presented extended half-life FVIII and FIX products are primarily summed up.

What exactly will be the impact of the half-life extension on the clinical practice is described from page 32 onwards, including different scenarios.

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Emicizumab (ACE910)

Once weekly prophylaxis with emicizumab (administered subcutaneously) showed good efficacy in individuals with severe haemophilia A and inhibitors\(^1\). The drug will be licensed in Europe for treatment of these patients in the coming months.

Gene Therapy

Clinically significant factor levels have been achieved, even in patients who mounted an immune response to viral vectors. This response remains a serious obstacle in some studies.\(^2\) Yet, phase III studies of gene therapies for both haemophilia A and B will soon commence.

Some patients achieved sustained high factor levels, which made replacement therapy with factor substitution unnecessary. To maintain factor production in the liver, some patients who show immune response to vectors may require treatment with cortisone.

In the case of haemophilia A, the first promising results with this technology were presented in 2016.\(^3\)

Pros:

- Reduced frequency of infusions
- Better protection against bleeding and joint damage
- Better adherence to prophylaxis

Cons:

- Immune response
- Allergic reactions

Difficult laboratory monitoring

Potential accumulation of PEG in the body

Adverse events may occur that might be difficult to prepare for and respond to

Gene therapy cannot be repeated with the same vector

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Different scenarios for using products with extended half-life

In the following section, three possible scenarios of prophylaxis with extended half-life rFVIII and an example for rFIX are shown. The choice of treatment regimen should be made jointly by the patient and the physician based on the individual clinical picture.

A patient with FVIII deficiency with a lot of breakthrough bleeds, for example, may not benefit from less frequent infusions, since it would waste an opportunity to achieve better protection of the patient from bleeding. On the other hand, a patient with FVIII deficiency who experiences few spontaneous bleeds on prophylaxis with standard half-life products may do well on fewer infusions and consume less factor while enjoying the same level of protection.

The example of using EHL FIX for haemophilia B presented at the end involves reducing the number of injections from two to one per week. However, the intervals between infusions may be extended to 10 or even 14 days, with appropriate dosage adjustment.

In terms of weighing all the different needs and aspects of care (venous access, adherence, bleeding tendency etc.), it seems reasonable to choose the longest possible prophylaxis interval with the new products, as long as it does not compromise the protection from bleeding.

 Fewer infusions per week with the same dose (haemophilia A)

→ Frequency of injections
  - reduced from 3x weekly to 2x weekly

→ Dosage
  - extended rFVIII: 2 x 35 IU / kg per week (e.g., Monday, Thursday)
  - conventional FVIII: 3 x 35 IU / kg per week (e.g., Monday, Wednesday, Friday)
  - reduced weekly consumption

→ The same trough level and fewer injections (presumably the same protection against spontaneous bleeding)

![Graph showing FVII activity over time with different dosing regimens]

Fewer infusions per week with higher dose (haemophilia A)

- Frequency of injections
  - reduced from 3x weekly to 2x weekly

- Dosage
  - extended rFVIII: 2 x 50 IU / kg per week (e.g., Monday, Thursday)
  - Conventional FVIII: 3 x 35 IU / kg per week (e.g., Monday, Wednesday, Friday)
  - Approximately the same weekly consumption

- Higher trough levels and fewer injections (presumably higher protection against spontaneous bleeding)

The same treatment regimen with the same dose (haemophilia A)

- Frequency of injections
  - 3x weekly

- Dosage
  - extended rFVIII: 3 x 35 IU / kg per week (e.g., Monday, Wednesday, Friday)
  - Conventional FVIII: 3 x 35 IU / kg per week (e.g., Monday, Wednesday, Friday)
  - the same weekly consumption

- Much higher trough levels with the same number of injections (presumably significantly higher protection against spontaneous bleeding)

Fewer infusions per week with the same dose (haemophilia B)

- Frequency of infusions
  - reduced from 2x weekly to 1x weekly

- Dosage
  - extended rFIX: 1x 50 IU/kg per week (e.g., Monday)
  - conventional rFIX: 2x 50 IU/kg per week (e.g., Monday, Thursday)
  - reduced weekly consumption

- The same trough level and fewer infusions (presumably the same protection against spontaneous bleeding)

Summary

![Graph showing FIX activity in plasma over time for extended and conventional rFIX dosages.](image-url)
Various technologies have been developed to extend half-life.

Since 2016, two rFIX and three rFVIII have already been licensed and available in Europe.

Further products will be licensed from 2018 onwards.

The half-life can be extended
- Factor IX: approximately 5-fold / 1 infusion every 1-2 weeks
- Factor VIII: approximately 1.5 fold / 2 infusions per week

Improvement in treatment outcomes is the main goal
- higher factor levels / better protection
- less spontaneous bleeding
- better treatment adherence / less dependence on therapy

Non-replacement therapies will be available in the medium term.
Note of thanks

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16. Lacroix A. Blood 2015;126(9):1078-245924561.html; most recently accessed on 23 February 2017.


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<td><strong>Antithrombin (AT)</strong></td>
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<td><strong>Episomes</strong></td>
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<td><strong>Fusion proteins</strong></td>
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In contrast to the antigen-binding Fab fragment, the Fc fragment is a conserved part of the antibody.

**Fc region**

*FcRn* neonatal Fc receptor, a cell surface protein, which recognizes the Fc fragment of immunoglobulin G and albumin, and recycles them back to the circulation. This mechanism is used to extend half-lives of clotting factors by fusing them with the Fc fragment or albumin.

**Clotting factors**

are enzymes or cofactors (mostly proteins) which form complexes in the presence of Ca-ions to promote blood clotting.

**Glycans**

Also referred to as polysaccharides, are carbohydrates in which a large number (at least ten) monosaccharides (single sugars) are linked via glycosidic bonds.

**Haemophilia**

is a congenital lifelong bleeding disorder caused by a deficient activity of the clotting factor VIII (haemophilia A) or IX (haemophilia B).

**IgG1**

a subclass of IgG

**Immunoglobulins**

are endogenous proteins which defend from infections

**Immunoglobulin G**

antibodies are divided into different classes, one of them being immunoglobulin G

**Covalent Bond**

a strong chemical bond between two molecules

**Cryoprecipitate**

By freezing and thawing blood plasma, a precipitate (cryoprecipitate) is formed, which can be separated from the rest of the plasma by centrifugation. The proteins which are important for blood clotting, factor VIII, von Willebrand factor and fibrinogen accumulate in the cryoprecipitate

**Mimetic**

is based on the principle of imitation

**mRNA**

messenger RNA

**N-acetylgalactosamine**

is a type of sugar and a building block of carbohydrate parts of glycolipids and glycoproteins

**N-glycans**

complex carbohydrate chains linked to a specific amino acid side-chain (asparagine) in the protein

**O-glycans**

complex carbohydrate chains linked to a specific amino acid side-chain (serine or threonine) in the protein

**Pasteurisation**

considerate heating of plasma products (e.g. 10 hours at 60 °C) to inactivate viruses vulnerable to heat treatment

**PEG**

typically polyethyleneglyco

**PEGylation**

in the so-called PEGylation, bio-pharmaceutical active substances or diagnostics are chemically combined (conjugated) with polyethylene glycol (PEG). Chain-shaped structures are attached to the active substance or the diagnostic agent, almost completely enveloping them and thus reliably protecting them against the premature degradation by endogenous enzymes, for example proteases

**Plasma derivatives**

Biological medicines manufactured from the human blood plasma

**Polyethylene glycol**

liquid or solid, chemically inert, water-soluble and non-toxic polymer

**Polysialic acid**

is an "acidic sugar" that, as a component of the glycocalyx, is responsible for the negative charge of all animal cells
| **Recycling** | Here used to describe the redirection of Fc or albumin fusion proteins to the bloodstream following uptake by tissues |
| **Recombinant** | produced by recombinant DNA technology. For example, recombinant factor VIII concentrates, are manufactured using hamster or human cell lines in a growth medium and purified by elaborate methods. |
| **Renal clearance** | excretion via the kidney |
| **Ribosome** | a part of the machinery employed by the cells to synthesize proteins. Proteins are produced in the cells according to the nucleotide sequence of the deoxyribonucleic acid (DNA), which contains the information on the amino acid sequence of the proteins |
| **RISC** | RNA-induced silencing complex; Complex of RNA and proteins. The production of specific proteins is switched off (gene knockout) or decreased (gene knockdown), while the complex is degrading the mRNA coding for these proteins or inhibiting their translation to the protein |
| **RNA/RNS** | ribonucleic acid, a complex molecule, whose main function is conversion of genetic information into proteins |
| **RNAi** | RNA interference (RNAi or RNA silencing) is an important natural mechanism of gene silencing in the cells of living organisms with a cell nucleus (eukaryotes). |
| **siRNA** | Small interfering RNA, abbreviated siRNA, are short, single-stranded or double-stranded ribonucleic acid molecules of 20 to 25 base pairs length. They do not encode proteins, but bind with complementary single-stranded ribonucleic acid molecules, thus preventing their normal function |
| **Substitution** | Replacement/administration of factor concentrates |
| **Subcutaneous** | Injected under the skin |
| **TFPI** | Tissue Factor Pathway Inhibitor is a single chain polypeptide that can reversibly inhibit factor Xa. While Xa is inhibited, the Xa-TFPI complex can also inhibit the FVIIa-tissue factor complex |
| **Thrombin** | Thrombin (factor IIa) is the most important enzyme of blood clotting and breaks fibrinogen down to fibrin |
| **Viruses** | Viruses are infectious particles which can spread as virions outside cells (extracellularly) by transmission but can only multiply as viruses within a suitable host cell (intracellularly) |
| **XTEN** | is a polypeptide that can be metabolized by the body. By introducing XTEN into proteins, e.g. clotting factors, their half-life can be prolonged |
If you have any questions, please contact the office of your patient association.

Publisher

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