Coagulation Disorders

Haemophilia A (classic haemophilia) is an X-chromosome-linked bleeding disorder occurring in approximately one in 5,000–10,000 males worldwide.\(^2\) Haemophilia A is caused by a partial or total deficiency of functionally active coagulation factor VIII (FVIII). Haemophilia produces abnormal bleeding that may be mild, moderate or severe depending on the degree of FVIII deficiency. Individuals with severe haemophilia A have FVIII levels <1% of normal activity (<0.01IU/ml), whereas moderate (factor level 0.01–0.05IU/ml) to mild (factor level >0.05–0.40IU/ml) forms have 1–5% and 5–40% of normal activity, respectively.\(^1\) In patients with severe haemophilia A, the first bleeding typically occurs during early childhood. The bleeding can involve any anatomical region but most commonly involves the joints (frequently elbows, knees and ankles) and muscles. Joint haemorrhages can result in severe arthropathy and degenerative damage, as found in osteoarthritis, as well as inflammatory processes similar to rheumatoid arthritis.\(^3\) In contrast to severe haemophilia A, which is characterised by spontaneous bleeding, mild haemophilia A may go undiagnosed until adulthood due to the lack of spontaneous bleeding. The diagnosis of haemophilia A is confirmed by the finding of normal platelet count and function, normal bleeding time, normal prothrombin time and normal von Willebrand factor (VWF). FVIII binding activity is present, but there is prolonged activated partial thromboplastin time (aPTT) and reduced FVIII activity (FVIII:C).\(^1,2\) The diagnosis is completed by molecular genetic testing to identify the genetic defect.

Haemophilia A is incurable, but treatment with antihaeomophilic therapy can stop or prevent bleeding episodes, reduce the associated morbidity, improve quality of life and normalise life expectancy. For patients with mild haemophilia A, treatment with desmopressin (DDAVP) is usually sufficient to manage bleeding episodes.\(^2\) However, for patients with mild haemophilia A who do not respond adequately to DDAVP, and for those with moderate or severe forms of the disease, replacement of the deficient factor with commercially prepared FVIII concentrates is generally required. Infusion of these concentrates temporarily increases the plasma level of FVIII and improves clinical symptoms when given on demand for bleeding episodes or during emergency situations or prophylactically to prevent spontaneous bleeding (e.g. in severe haemophilia) or for elective surgery.

Two different types of FVIII concentrates are available for treatment: concentrates purified from donated plasma, with or without VWF, and FVIII products manufactured with recombinant technologies and purified from cell-culture harvest medium. In the past 25 years, advances in the screening of donors and donated plasma, techniques to remove and/or inactivate viruses in concentrates and recombinant technology have remarkably increased the safety and purity of FVIII products. In addition to the full-length FVIII products, a B-domain-deleted (BDD) recombinant FVIII (rFVIII) concentrate that shows clinical haemostatic efficacy in patients with haemophilia A has been developed.\(^4,5\) More recently, an rFVIII product has been developed without the use of human or bovine albumin with the aim of further eliminating the potential risk of viral transmission.\(^6\) In addition to the risk of viral transmission, other product characteristics such as efficacy, tolerability, immunogenicity (development of inhibitors), dosage and administration are also considered when selecting a treatment option for patients with haemophilia A. This article summarises the available evidence for these characteristics of recombinant antihaeomophilic factor products for managing haemostasis in patients with moderate/severe haemophilia A.

Recombinant Antihaeomophilic Factor Products

Product Specifics

Several recombinant antihaeomophilic products — including Recombinate™ (Baxter Healthcare),\(^7\) Kogenate® Bayer (Kogenate® FS; Bayer Healthcare),\(^8\) Helixate®HexGen (Helixate® FS; Bayer Healthcare, distributed by CSL Behring),\(^9\) ReFacto® (Wyeth Pharmaceuticals)\(^10\) and Advate™ (Baxter Healthcare)\(^11\) (see Tables 1 and 2) — are commercially available for the treatment of haemophilia A. These are categorised according to their product characteristics, including:

- type of host cell and production details;
- degree of purity;
- viral removal/inactivation processes; and
- presence/absence of animal proteins or human albumin.

Purity and Formulation

There is wide variability among the rFVIII concentrates with respect to final product purity, as reflected by units of specific activity (IU FVIII:C) per milligram of total protein (see Table 2). ‘Purity’ refers to the amount of desired ingredient (FVIII) relative to other protein ingredients (such as albumin as stabiliser). These products contain between 2,000 and 13,000 units of FVIII activity per milligram of protein depending on the type of FVIII molecule (full-length versus BDD), the purification process and whether or not albumin is used as a stabiliser. The currently available rFVIII products are considered very safe as a result of the inclusion (in most of them) of improved virus inactivation and removal steps in the manufacturing process, which minimises the risk of infection from plasma-based additives and DNA technology. The methods currently in use include:

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Coagulation Disorders

Haemophilia

### Table 1: Properties of Recombinant Antihaemophilic Factor VIII Concentrates

<table>
<thead>
<tr>
<th>Property of rFVIII Product</th>
<th>Recombinate™</th>
<th>Kogenate® Bayer/Helixate® NexGen</th>
<th>ReFacto®</th>
<th>Advate™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generation</td>
<td>First</td>
<td>Second</td>
<td>Third</td>
<td>Third</td>
</tr>
<tr>
<td>FVIII molecule</td>
<td>Full-length</td>
<td>Full-length</td>
<td>B-domain-deleted</td>
<td>Full-length</td>
</tr>
<tr>
<td>Cell line</td>
<td>CHO</td>
<td>CHO</td>
<td>CHO</td>
<td>CHO</td>
</tr>
<tr>
<td>FVIII stabiliser</td>
<td>Human albumin</td>
<td>Sucrose</td>
<td>Sucrose</td>
<td>Trehalose</td>
</tr>
<tr>
<td>Animal/human plasma proteins in cell medium</td>
<td>Yes (bovine)</td>
<td>Yes (human)</td>
<td>Yes (human)</td>
<td>No</td>
</tr>
<tr>
<td>Animal/human plasma proteins in purification and final formulation</td>
<td>Yes (human)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

**MAbs** = monoclonal antibodies.

- **Virus inactivation:**
  - 2 x ion-exchange chromatography
  - Immunoaffinity chromatography
  - Gel filtration
  - Immunoaffinity chromatography on MAbs

- **Viral elimination:**
  - 2 x ion-exchange chromatography
  - Gel filtration
  - Immunoaffinity chromatography on MAbs
  - Three other chromatographies

- **Technology:**
  - Recombinant
  - Plasma/albumin-free recombinant

- **Purity:**
  - >4,000 IU/mg protein (much less including albumin)
  - >4,000 IU/mg protein
  - Up to 13,000 IU/mg protein
  - >4,000 IU/mg protein

- **Viral removal method:**
  - 2 x ion-exchange chromatography
  - Immunoaffinity chromatography on MAbs
  - Gel filtration
  - Immunoaffinity chromatography on MAbs

- **Viral inactivation method:**
  - No specific method
  - Solvent/detergent
  - Solvent/detergent

- **Half-life:**
  - 14.6 ± 4.9 hours
  - 13 hours
  - 14.8 ± 5.6 hours
  - 11.98 ± 4.3 hours

- **In vivo recovery:**
  - 2.4% IU/dl/IU/kg
  - 2.1 ± 0.3% IU/kg
  - 2.4 ± 0.4% IU/dl/IU/kg
  - 2.4% IU/dl/IU/kg

- **Diluent volume:**
  - 10ml sterile water
  - 2.5ml sterile water
  - 4ml sodium chloride
  - 5ml sterile water

- **Indication:**
  - Haemophilia A
  - Haemophilia A with deficiency of FVIII
  - Haemophilia A prevention/ control haemostasis
  - surgical prophylaxis
  - short-term routine prophylaxis
  - Haemophilia A
  - peri-operative management of haemostasis

- **Technology:**
  - Recombinant
  - Recombinant
  - Recombinant
  - Plasma/albumin-free recombinant

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  - CHO
  - CHO
  - CHO
  - CHO

- **FVIII molecule:**
  - Full-length
  - Full-length
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  - Full-length

- **FVIII stabiliser:**
  - Human albumin
  - Sucrose
  - Sucrose
  - Trehalose

- **Animal/human plasma proteins in cell medium:**
  - Yes (bovine)
  - Yes (human)
  - Yes (human)
  - No

- **Animal/human plasma proteins in purification and final formulation:**
  - Yes (human)
  - No
  - No

### Table 2: Characteristics of Recombinant Antihaemophilic Factor VIII Concentrates

<table>
<thead>
<tr>
<th>Characteristic</th>
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<th>ReFacto®</th>
<th>Advate™</th>
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  - Yes (human)
  - Yes (human)
  - No

- **Animal/human plasma proteins in purification and final formulation:**
  - Yes (human)
  - No
  - No

### Efficacy

It is not possible to make direct comparisons of haemostatic efficacy between the different antihemophilic factor VIII products due to the lack of comparative clinical trials. There is only one published study that has directly compared the pharmacokinetics of Advate with those of ReFacto.12 This study did not observe any significant differences between the two products. Data from pivotal trial programmes and post-marketing surveillance studies additionally support the impression that the currently available rFVIII products are equally effective and similar to the established plasma-derived (pd) products in preventing and controlling bleeding episodes in patients with haemophilia A (primarily in those with moderate or severe disease). In most cases, one or two single bolus infusions of the antihemophilic factor concentrate result in efficacy ratings of ‘excellent/good’ in over 85% of patients, including paediatric14 and adult patients, previously untreated patients (PUPs), minimal treated patients (MTPs)16,18 and previously treated patients (PTPs).5,19–23 The case is the same for those undergoing surgical or invasive procedures,24–26 those receiving prophylaxis7,27 and those in long-term and home treatment settings.19,28,29 Furthermore, continuous infusion therapy with some rFVIII products has demonstrated efficacy ratings of ‘excellent/good’ in the majority of haemophilia A patients.19,20–32 More recently, prophylactic infusions of rFVIII have demonstrated significant reductions in the incidence of not only bleeding episodes but also joint haemorrhages and the associated joint damage of young children with severe haemophilia A.33

### Safety

#### Adverse Events

Since the development of the first rFVIII product in 1992, all rFVIII products have been assessed extensively regarding their safety and tolerability profiles. Adverse events, which are similar among the rFVIII products, are generally infrequent and mild in nature and include headache, nausea, dizziness, fever, lethargy and altered taste.3,15–17 Allergic reactions are rare for all products. In pivotal trial programmes and post-marketing surveillance studies, the majority of physicians and/or patients...
As part of our passion and commitment we strive to improve the quality of life for people with rare coagulation disorders.

CSL Behring is proud to provide the broadest range of therapeutic options even beyond hemophilia and von Willebrand disease.

The long track records document our successful efforts to make effective and safe treatments available.

Factors for Life
Coagulation Disorders

### Coagulation Disorders: Haemophilia

#### Table 3: Factors Affecting the Occurrence of Factor VIII Inhibitors in Patients with Haemophilia A

<table>
<thead>
<tr>
<th>Factor</th>
<th>Occurrence of Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of haemophilia</td>
<td>More common in patients with severe haemophilia than those with either mild or moderate forms of the disease.</td>
</tr>
</tbody>
</table>
| Mutation type and severity    | Occur in 30–40% of patients with mutations that prevent the formation of FVIII such as:  
- gene deletions;  
- non-sense mutations causing premature stop codons; and  
- FVIII gene inversions. |
| Family history                | More common in those with a family history of inhibitors. |
| Ethnicity                     | More common in Africans than Caucasians. |
| Other                         | May be affected by:  
- intensity of first treatment;  
- mode of treatment (prophylaxis versus on-demand);  
- age at first treatment;  
- type of haemorragic;  
- type of FVIII concentrate (pd-FVIII versus rFVIII);  
- switching FVIII products; and  
- length of treatment. |

#### Table 4: Occurrence of Inhibitors to Factor VIII with Recombinant Factor VIII Concentrates in Patients with Haemophilia A

<table>
<thead>
<tr>
<th>Patient</th>
<th>Recombinate™</th>
<th>Kogenate®</th>
<th>Bayer®</th>
<th>NexGen®</th>
<th>ReFacto®</th>
<th>Advate™</th>
<th>PTPs</th>
<th>PUPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTPs</td>
<td>2.9%</td>
<td>&lt;2%</td>
<td>2.8%</td>
<td>0.9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PUPs</td>
<td>30%</td>
<td>15%</td>
<td>32%</td>
<td>NA*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NA* = data currently not available as clinical trial in PUPs is still ongoing. PTPs = previously treated patients; PUPs = previously untreated patients.

#### Risk of Viral Transmission

The risk of transmission of blood-borne viruses, including human immunodeficiency virus (HIV), hepatitis B (HBV) and hepatitis C (HCV) viruses, as well as bacteria and protozoans by contaminated plasma products, has virtually been eliminated by introducing comprehensive safety measurements. In addition, in all but one of the currently marketed rFVIII products, a solvent/detergent inactivation step was introduced to inactivate enveloped viruses that theoretically might be in the harvest medium as a contaminant from the cell culture or from the plasma additives. Nevertheless, the third-generation rFVIII product was developed to offer the additional advantage of being manufactured in an albumin- and plasma-free medium, which is thought to even further reduce the risk of transmitting blood-borne pathogens. All of these measures guarantee a very high level of pathogen safety for the rFVIII products.

#### Dosage and Administration

Dosing regimens for FVIII concentrates in haemophilia are generally based on in vivo recovery (IVR) and biological half-life. IVR is the ratio of the observed peak factor concentration to the predicted peak factor concentration, and can vary depending on the patient’s plasma volume and dose of factor. The currently available rFVIII products result in a rise of at least 2% per IU/kg of infused factor (see Table 1). The published product half-lives range from almost 12 hours with Advate to almost 15 hours with ReFacto. The diluted volumes range from 2.5ml (Kogenate Bayer/Helixate NexGen) to 10ml (Recombinant) per vial, with some vials containing different potencies of product. The smaller the diluted volume, the more convenient the administration, due to less time needed for infusion of the highly concentrated products. The dose and duration of therapy with rFVIII concentrates depends on the site, size and severity of the bleeding episode, presence of inhibitors, previous anamnestic response, desired FVIII level and the individual needs of the patient. Replacement factor products are administered as intravenous bolus infusions for the majority of bleeding episodes. However, for surgical prophylaxis, continuous infusion of FVIII concentrates may be the preferred treatment approach. Continuous infusion regimens offer the potential for cost and product savings owing to better steady-state pharmacokinetics, the need for less product and a more convenient and simplified treatment option by eliminating the need for frequent bolus injections and blood sampling. Kogenate Bayer/Helixate NexGen is the only rFVIII product that has received European approval for use as a continuous infusion for patients with haemophilia undergoing major surgery.
Choice of Recombinant Factor VIII Product

Recombinant FVIII products have become accepted alternatives to the established plasma-derived concentrates for the treatment of haemophilia A and thereby continue the trend of the last 20 years towards higher purity and specificity. All of the commercially available recombinant antihemophilic factor products demonstrate similar ‘excellent/good’ haemostatic efficacy and similar tolerability in patients with moderate or severe haemophilia A. The safety profiles of these products are also similar, although one of the products has no virus inactivation implemented and the overall reported risks of inhibitor formation in PUPs is different and by far the lowest with Kogenate Bayer/HelixateNexGen, but similar between all products in PTPs. Dose and administration are also considerations for selecting a treatment option; features such as viable/diluent size, ease/convenience of administration, intensity of treatment (such as continuous infusions) and reconstitution/delivery system all contribute to the final decision.

Other factors that influence treatment choices include cost, availability and patient/physician preference.