Human FVIII naturally stabilised with VWF

Success is Overcoming Challenges in Life
octanate® at a glance

- Human plasma derived coagulation factor VIII (FVIII) naturally stabilised with von Willebrand factor (VWF)

- Low immunogenic with low levels of inhibitor formation in previously untreated patients (PUPs)

- No inhibitors found or reported in previously treated patients (PTPs)

- High levels of efficacy in inhibitor elimination via Immune Tolerance Induction (ITI)

- Every FVIII molecule is bound to and protected by VWF

- Absence of immunogenic “danger signals” *

- VWF:RCo/FVIII:C ratio is approximately 0.4

- High-purity, no albumin added as a stabiliser (specific activity ≥ 100 IU/mg protein)

- 250, 500 and 1000 IU vials for reconstitution with 5ml (250 IU) or 10ml (500 and 1000 IU) Water for Injections (50/100 IU/ml)

- Excellent clinical efficacy and tolerability

- Double virus inactivation by solvent/detergent and terminal dry-heat treatment to inactivate both enveloped and non-enveloped viruses

- Indicated for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital FVIII deficiency)

- Safely used since 1998 with no proven cases of life-threatening virus transmissions after > 3 billion IU infused

- Available in 67 countries world wide

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* absence of antigenic N-glycolycoeuraminic acid (NeuGc) or Gal-a(1,3)Gal epitopes which are present in recombinant FVIII (rFVIII) derived from hamster cell-lines.1)

1) Thrombosis and Haemostasis (Schattauer GmbH). Loose insert, distributed in association with the February 2010 issue
Human FVIII naturally stabilised with VWF

octanate® is a human-derived, high-purity, freeze-dried, double virus-inactivated FVIII concentrate for intravenous administration. All coagulation FVIII present in octanate® is bound to its natural stabiliser, von Willebrand factor (VWF), in a VWF/FVIII ratio of approximately 0.4. Therefore, no additional stabilisers are required during the manufacture of octanate®. octanate® is used in the treatment of bleeding in patients with all types of haemophilia A.

octanate® is manufactured from human plasma. The high requirements for virus safety are fulfilled by the combination of two effective methods of virus inactivation; solvent/detergent (S/D) treatment using TNBP and Polysorbate 80 and terminal dry heat treatment of the lyophilised product. These process steps are aggressive enough to inactivate viruses efficiently, yet gentle enough to maintain the structural integrity and function of the VWF and FVIII molecules, as proven by state-of-the-art assays covering the diverse features of its importance.

octanate® is one of the most widely used VWF-stabilised FVIII products worldwide:

- octanate® was first approved in Germany in August 1998 and has since been approved in 67 countries.
- Between August 1998 and February 2010, a total of approximately 3.2 billion IU octanate® have been distributed worldwide. Assuming a mean daily dosage of 1,500 IU, this equates to roughly 2.2 million exposure days (EDs) of usage in patients.

octanate® dissolved in Water for Injections

<table>
<thead>
<tr>
<th>Fill size (IU)</th>
<th>Solvent volume ml (Water for Injections)</th>
</tr>
</thead>
<tbody>
<tr>
<td>octanate® 250</td>
<td>5</td>
</tr>
<tr>
<td>octanate® 500</td>
<td>10 *</td>
</tr>
<tr>
<td>octanate® 1000</td>
<td>10 **</td>
</tr>
</tbody>
</table>

* octanate® 500 in 5 ml is currently under development.
** octanate® 1000 in 5 ml is already available in Germany and will be on the market in other countries shortly.

octanate® 1000 composition

| Mean VWF:RCo/FVIII:C IU/IU (chromogenic assay) | 0.4 |
| Mean specific activity FVIII:C/mg protein     | 115 |

1) Data on file – Octapharma company internal report (average of 65 batches)

High purity and retention of the FVIII physiological function is the basis for the efficacy and tolerability of octanate®

octanate® is available in 250 IU, 500 IU and 1000 IU presentations.

The mean specific activity of octanate® is ≥ 100 IU/mg protein. Due to its high purity, the patient receives a far lower amount of undesired foreign protein – (approximately 1/10) – compared to preparations stabilised with albumin.

octanate® is effective and well-tolerated, owing to its nativity and unaltered physiological function. Clinical studies support the efficacy and tolerability in the treatment of bleeding and in prophylaxis.
Human FVIII naturally stabilised with VWF

FVIII fully protected by VWF – what belongs together stays together

The von Willebrand factor (VWF) in plasma forms a complex with FVIII and protects it against undesired activation and premature proteolytic degradation. The VWF serves as a transport protein and concentrates FVIII at the site of injury. In addition, VWF imparts to FVIII the correct structure and modulates its secretion. FVIII is physiologically stabilised by its binding to VWF.

Where there is no binding to VWF, the half-life of FVIII is reduced from approximately 14 to 3 hours. Since the FVIII/VWF complex is preserved in the manufacturing process of octanate®, the VWF fulfils its function as a physiological stabiliser of FVIII.

The interaction of FVIII with VWF is of direct clinical significance in the diagnosis and treatment of patients with haemophilia A(1,2).

The importance of VWF in the FVIII life cycle and activity(1–3)

VWF plays a key role in:

Reduced FVIII immunogenicity
- prevents the binding of FVIII to antigen-presenting cells (APC) and thereby subsequent presentation to immune effectors

FVIII production and conformation
- modulates FVIII secretion and ensures the correct structure

FVIII stabilisation
- protects FVIII from undesired activation and premature proteolytic degradation
- increases the circulatory half-life of FVIII

FVIII transport
- transports FVIII to the bleeding site where coagulation is needed

FVIII function
- increases FVIII susceptibility to thrombin cleavage
- decreases FVIII susceptibility to activated protein C and activated FIX
- prevents phospholipid binding
FVIII contains three distinct domains A, B, and C arranged in the order A1-A2-B-A3-C1-C2. A major VWF-binding site is located on the amino-terminal region of the FVIII light chain corresponding to the A3, C1 and C2 domains.

### Structure of the FVIII molecule – showing A, B, and C domains.
Adapted from ref. (4), with permission, © 1994 Massachusetts Medical Society. All rights reserved.

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**In octanate®**
- FVIII and VWF form a tightly bound, intact complex
- VWF possesses additional binding – and stabilising capacity for FVIII

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**The FVIII/VWF complex plays a critical role in mediating primary haemostasis and coagulation**

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**All FVIII in octanate® is bound to and protected by VWF**

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octanate® – highly successful in FVIII inhibitor eradication

With serious viral transmission now fully under control, the most serious clinical complication of FVIII replacement therapy is the risk of developing inhibitory antibodies to FVIII, rendering the patient resistant to replacement therapy and thereby increasing the risk of unmanageable bleeding, in particular arthropathy, and disability\(^1\). Inhibitors arise in up to 40% of previously untreated severe haemophilia A patients\(^2\). Presence of an inhibitor thereby not only has major adverse implications for quality of life, but also impacts dramatically on the cost of care, increasing overall treatment expenditures 3 – 5 fold\(^3\).

Immune tolerance induction (ITI), involving repeated and persistent treatment with FVIII replacement is the only proven strategy for FVIII inhibitor eradication. Successful tolari-sation allows resumption of fully-effective on-demand replacement treatment and prophylaxis, with a consequent improvement in patient quality of life and estimated savings of US $1.7 million over a lifetime\(^4\).

Since January 2006, 46 inhibitor patients have been treated with octanate® for ITI in the frame of the ongoing Observational Immune Tolerance Induction (ObsITI) research study (www.obsiti.com) at 11 centres. All patients are followed up prospectively. 18 patients have already completed the ObsITI study.*

83.3% ITI success rate in inhibitor patients treated with octanate® despite the stringent success criteria\(^5\)

<table>
<thead>
<tr>
<th></th>
<th>100</th>
<th>80</th>
<th>60</th>
<th>40</th>
<th>20</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete success</td>
<td>77.8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>5.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>16.7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n=18 total patients

<table>
<thead>
<tr>
<th></th>
<th>2 low-responders (LRs): median inhibitor titre at a baseline of 1.18 BU</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 high-responders (HRs): median inhibitor titre at a baseline of 12.4 BU</td>
<td></td>
</tr>
<tr>
<td>72.2% of the patients had at least one poor-prognostic factor for ITI failure</td>
<td></td>
</tr>
<tr>
<td>33.3% of the patients had undergone previous ITI attempts and failed</td>
<td></td>
</tr>
</tbody>
</table>

* “completed” refers to patients who have achieved complete success, who have completed 36 months of the observational study period or have finished ITI treatment based on the investigator’s decision.
**ITI treatment flowchart with octanate**

- **ITI start**
  - Criterion I: Inhibitor titre < 0.6 BU
  - Criterion II: Normalised FVIII recovery
  - Criterion III: Normalised FVIII half-life

- **Partial response**
- **Partial success**
- **Complete success**
- **Completed ITI**
- **End of the study period**

**Ongoing ITI (36 months)**

- **Monitoring for relapse**

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- The success criteria defined in the ObsITI study are more stringent than to the consensus criteria (inhibitor titre < 0.6 BU, FVIII:C IVR ≥ 66% and FVIII:C t½ ≥ 6 hours) agreed by the European Haemophilia Therapy Standardisation Board (EHTSB) in 2006, which were also used in the recently halted I-ITI study.\(^{6,7}\)

- **Prophylaxis for 12 months**

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**All patients were treated with octanate** according to the Bonn Protocol as follows:

- **LRs**: 50 – 100 IU octanate\(^*\)/kg daily or every other day
- **HRs**: 100 – 150 octanate\(^*\)/kg every 12 hours

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**Successful ITI outcome even in poor prognosis patients**

**No relapses after successful ITI**

**Successful ITI outcome in poor prognosis patients in a mean time of less than 1 year**

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octanate® and low occurrence of inhibitors

Incidence of inhibitors in PUPs with severe haemophilia A (%)

- Low incidence (5.1%) of inhibitor incidence in a prospective clinical trial with previously untreated patients (PUPs)\(^1\)
- In prospective clinical studies, no inhibitor formation observed in previously treated patients (PTPs)\(^7\text{–}^{12}\)

5% Inhibitor incidence in PUPs

- octanate\(^\circledR\)\(^{(1)}\)
  - 5.1% (n = 39)
- kogenate FS\(^{(2)}\)
  - 15% (n = 60)
- kogenate\(^{(3)}\)
  - 29.2% (n = 65)
- refacto\(^{(4)}\)
  - 31.7% (n = 101)
- recombinant\(^{(5)}\)
  - 28% (n = 50)
- recombinant\(^{(6)}\)
  - 31.5% (n = 73)

Human FVIII naturally stabilised with VWF
In previously untreated patients (PUPs)

Since 2000, 39 PUPs with severe haemophilia A (n = 36 ≤ 1 % FVIII:C; n = 3 ≤ 2 % FVIII:C), mainly treated on-demand, have been included in an ongoing good clinical practice (GCP) study⁴.

FVIII mutation analysis*  

* Patients with intron 22 inversion and, thus, no endogenous FVIII synthesis, have a substantially higher inhibitor incidence than patients with milder molecular defects. It would be expected that between 30 and 35% of all intron 22 inversion patients develop inhibitors after exposure to exogenous FVIII⁵. Therefore, amongst the 16 subjects in this study, it would be reasonable to expect 5 or 6 subjects to develop an inhibitor.

![Mutation Analysis Graphic](https://via.placeholder.com/150)

### Population demographics and baseline characteristics (n = 39)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n = 39</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age – median; range (years)</strong></td>
<td></td>
</tr>
<tr>
<td>At study enrolment</td>
<td>0.7; 0.0 – 5.6</td>
</tr>
<tr>
<td>At diagnosis</td>
<td>0.6; 0.0 – 5.6</td>
</tr>
<tr>
<td><strong>Family history (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>53.9</td>
</tr>
<tr>
<td>Haemophilia A + inhibitors to FVIII</td>
<td>7.7</td>
</tr>
<tr>
<td><strong>FVIII:C (%)</strong></td>
<td></td>
</tr>
<tr>
<td>1 – 22%</td>
<td>7.7</td>
</tr>
<tr>
<td>≤ 1 %</td>
<td>92.3</td>
</tr>
<tr>
<td><strong>Prior vaccination (%)</strong></td>
<td></td>
</tr>
<tr>
<td>HAV</td>
<td>0.0</td>
</tr>
<tr>
<td>HBV</td>
<td>97.4</td>
</tr>
</tbody>
</table>

### Exposure days by reason of administration (n = 37)

<table>
<thead>
<tr>
<th>Reason for administration</th>
<th>EDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding episode</td>
<td>1470*</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td>78</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>1200</td>
</tr>
<tr>
<td>Study-related</td>
<td>55</td>
</tr>
<tr>
<td><strong>Total (all reasons)</strong></td>
<td>2801**</td>
</tr>
</tbody>
</table>

* On-demand treatment with octanate® accounted for over half of the EDs (n = 20 never received a prophylactic dose at all, n = 9 treated on-demand for ≥ 20 EDs prior to being switched to prophylactic administration). On-demand replacement therapy, i.e. starting and stopping treatment over long periods of time, as compared to continuous prophylaxis, has been associated with an increased risk of spontaneous inhibitor development⁶.

** Two subjects had exposures for 2 different reasons on the same day, each of which was counted as 1 ED overall.
Human FVIII naturally stabilised with VWF

75% of PUPs had more than 50 Exposure Days (EDs) to octanate®

- 16 (43%) > 100 EDs
- 12 (32%) 50 – 100 EDs
- 4 (11%) 20 – 49 EDs
- 5 (14%) 1 – 19 EDs

Prevention of inhibitors would be more efficacious from both a quality of life and a cost perspective rather than waiting to develop inhibitors and then attempting ITI\(^{(14)}\)

The inhibitor incidence with octanate® in PUPs is only 5.1%*

- 2 from 39 subjects (5.1%) developed clinically relevant inhibitors.
- Another 2 subjects displayed transient inhibitors which disappeared without an octanate® dosage change.
- All inhibitors developed before ED 50 were under on-demand treatment.
- No inhibitors were observed in PUPs receiving prophylaxis with octanate®

* Immunogenicity was assessed by the Bethesda assay according to Nijmegen modification with the cut-off 0.6 BU at baseline, and every 3 – 4 EDs up to the 20th ED, and thereafter every 10th ED until ED 100 or every 3 months, whichever comes first.
The inhibitor incidence with octanate® in PUPs is only 5.1%* from 39 subjects (5.1%) developed clinically relevant inhibitors. Another 2 subjects displayed transient inhibitors which disappeared without an octanate® dosage change. All inhibitors developed before ED 50 were under on-demand treatment. No inhibitors were observed in PUPs receiving prophylaxis with octanate®.

Due to the human origin of octanate®, “danger signals” like immunogenic N-glycoly neuraminic acid (NeuGc) or Gal-α(1,3)Gal epitopes observed with rFVIII derived from hamster cell-lines can be avoided.

VWF prevents the binding of FVIII to antigen-presenting cells such as macrophages and dendritic cells and thereby subsequent presentation of FVIII to immune effectors.\(^{15}\)\\

| Characteristics of subjects developing a clinically relevant FVIII inhibitor (n = 2) |
|---------------------------------|-----------------|-----------------|
| Subject | 1 | 2 |
| Type of inhibitors | high responding | high responding |
| EDs prior to detection | 6 | 3 |
| Treatment regimen | on demand | on demand |
| Genetic analysis | large deletion of exons 7 - 12 | intron 22 inversion |
| Family history of inhibitors | no | no |
| Inhibitor development | high responder (> 5 BU) | high responder (> 5 BU) |
| Max inhibitor titre (BU) | 328.0 | 445.0 |

octanate® is safe, well-tolerated and efficacious in the prophylaxis and treatment of bleeding in PUPs with severe haemophilia A and is associated with a minimal risk of inhibitors.

octanate® efficacy in PUPs (n = 1170 total bleeds)

- The haemostatic efficacy of octanate® in the prophylaxis and on-demand treatment of haemophilia A was assessed as “excellent”, irrespective of the indication for administration.
- 95.4% of the bleeds resolved within two days.
- Mean recovery was 2 %/IU/kg.
- In the surgical setting the efficacy was evaluated as “excellent” in all cases, with no complications reported.
In previously treated patients (PTPs)

Five prospective GCP studies with octanate® were conducted in 77 PTPs with severe haemophilia A (< 2 % FVIII:C) for the observational period of at least 6 months\(^{(7-12)}\)

- 4 GCP trials in patients > 12 years of age
- 1 GCP trial in children < 6 years of age
- All studies are finalised
- Total exposure days (EDs): 3,563
- Total octanate® dose, IU: 4,311,622
- Mean dose per patient, IU: 55,995
- Each pharmacokinetic study included a cross-over in which octanate® was found to be bio-equivalent with the respective preparations under comparison.

Demonstrated safety and efficacy in clinical trials with PTPs\(^{(7-12)}\)

- No inhibitors related to the treatment with octanate®*
- No virus transmission (HIV, HBV, HCV, Parvovirus B19)
- Very good tolerability
- Very good efficacy
- Successful use in surgery

* All patients were examined for inhibitors with the modified Bethesda assay at the start, and after 3 and 6 months of treatment. The recovery was measured at these times and followed up with the statistical evaluation of the recovery over time.
**Overview of EDs by reason of treatment in 5 clinical trials**

<table>
<thead>
<tr>
<th>Study design</th>
<th>Comparator for PK/result</th>
<th>No. of patients</th>
<th>Mean patient age in years (range)</th>
<th>Mean follow-up time on octanate® (weeks)</th>
<th>Inhibitor development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>Initial cross-over PK*, 6 month follow-up, final PK</td>
<td>10</td>
<td>29.6 (15 – 54)</td>
<td>28.5</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Monoclonally purifies pdFVIII/Bioequivalence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 2</td>
<td>Initial cross-over PK, 6 month follow-up</td>
<td>22</td>
<td>17.6 (11 – 38)</td>
<td>26.7</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>SD&amp;heat treated pdFVIII, Bioequivalence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 3</td>
<td>Initial cross-over PK, 6 month follow-up</td>
<td>12</td>
<td>30.8 (22 – 50)</td>
<td>25.5</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>octanate® from new production site, Bioequivalence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 4</td>
<td>6 months treatment</td>
<td>18</td>
<td>33.3 (18 – 49)</td>
<td>27.0</td>
<td>None</td>
</tr>
<tr>
<td>Study 5</td>
<td>1 to 2 years treatment</td>
<td>15</td>
<td>4.0 (1.1 – 5.9)</td>
<td>77.7</td>
<td>None</td>
</tr>
<tr>
<td>All studies</td>
<td>Prospective</td>
<td>77</td>
<td>22.3 (1.1 – 54)</td>
<td>36.7</td>
<td>None</td>
</tr>
</tbody>
</table>

* PK, Pharmacokinetic assessment

**Patients in total [n]**

| Mean recovery (range) [%/IU/kg] | 2.3 (1.8 – 3.1) |
| Mean half-life – T1/2 (range) [hours] | 12.2 (5.1 – 21.2) |

octanate® shows favourable FVIII half-life and recovery results in clinical studies investigating the PK profile of octanate®
More than 90% of the treatments were rated as "Excellent" or "Good". All initial "non-effective" treatments were finally resolved with octanate®

95.3% of all bleeding episodes resolved within 3 Days

octanate® is an efficacious, safe, well-tolerated, human plasma-derived, vWF-containing FVIII replacement product for the treatment of haemophilia A in PTPs

"Good" to "Excellent" haemostatic efficacy of octanate® in surgical procedures

- 19 surgical procedures in 14 patients (major n = 11; minor n = 8)
- The total doses used were adequate and effective for the type of procedure
- No unusual findings in blood loss or transfusion needs.
### Overview of Surgery Performed During Clinical Studies

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Surgery Type</th>
<th>octanate® Total Dose (IU)</th>
<th>Total Treatment/continuous Infusion Duration (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BT</td>
<td>21</td>
<td>Total hip replacement</td>
<td>45,978</td>
<td>20/12</td>
</tr>
<tr>
<td>KJ</td>
<td>19</td>
<td>Knee arthrodesis and orthopaedic fixation 5</td>
<td>52,000</td>
<td>19/19</td>
</tr>
<tr>
<td>KJ</td>
<td>20</td>
<td>Orthopaedic fixation removal</td>
<td>10,000</td>
<td>4/4</td>
</tr>
<tr>
<td>BP</td>
<td>38</td>
<td>Bilateral knee arthroplasty</td>
<td>41,300</td>
<td>26/8</td>
</tr>
<tr>
<td>BS</td>
<td>13</td>
<td>Achilles tendon extension</td>
<td>26,000</td>
<td>14/0</td>
</tr>
<tr>
<td>RK</td>
<td>11</td>
<td>Tooth extraction</td>
<td>1,000</td>
<td>1/0</td>
</tr>
<tr>
<td>IA</td>
<td>21</td>
<td>Total elbow replacement</td>
<td>70,000</td>
<td>19/19</td>
</tr>
<tr>
<td>LP</td>
<td>12</td>
<td>Liver biopsy</td>
<td>8,000</td>
<td>3/0</td>
</tr>
<tr>
<td>YA</td>
<td>25</td>
<td>Nail extraction</td>
<td>6,000</td>
<td>2/0</td>
</tr>
<tr>
<td>KS</td>
<td>33</td>
<td>Tooth extraction</td>
<td>3,000</td>
<td>1/0</td>
</tr>
<tr>
<td>WK</td>
<td>37</td>
<td>Multiple (6), unilateral tooth extraction</td>
<td>2,000</td>
<td>1/0</td>
</tr>
<tr>
<td>WK</td>
<td>37</td>
<td>Tooth extraction</td>
<td>3,000</td>
<td>1/0</td>
</tr>
<tr>
<td>GT</td>
<td>20</td>
<td>Cholecystectomy</td>
<td>38,000</td>
<td>13/13</td>
</tr>
<tr>
<td>GT</td>
<td>20</td>
<td>Tooth extraction</td>
<td>3,000</td>
<td>1/0</td>
</tr>
<tr>
<td>SW</td>
<td>13</td>
<td>Triplex – pes equino varus</td>
<td>23,000</td>
<td>13/0</td>
</tr>
<tr>
<td>SW</td>
<td>13</td>
<td>Kuerschner wire removal</td>
<td>3,000</td>
<td>8/0</td>
</tr>
<tr>
<td>MN</td>
<td>13</td>
<td>Liver biopsy</td>
<td>9,500</td>
<td>3/0</td>
</tr>
<tr>
<td>KK</td>
<td>26</td>
<td>Tooth extraction</td>
<td>3,000</td>
<td>1/0</td>
</tr>
</tbody>
</table>

1. Data on File – Interim Clinical Study Report AVI 403, Incidence of inhibitors in previously untreated patients with severe haemophilia A treated with octanate®.
7. Data on File – Final Clinical Study Report AVI 401, Pharmacokinetic properties, safety and efficacy of octanate® in previously treated patients with severe haemophilia A.
8. Data on File – Final Clinical Study Report AVI 402, Efficacy and safety of octanate® in previously treated patients with severe haemophilia A.
9. Data on File – Final Clinical Study Report AVI 401, 402 surgical documentation, efficacy and safety of octanate® in previously treated patients with severe haemophilia A.
10. Data on File – Final Clinical Study Report AVI 406, Pharmacokinetic properties of octanate®, manufactured at two production sites in previously treated patients with severe haemophilia A.
From selection to registration

- High requirements for the starting plasma
- Achieving the highest standards set in plasma sourcing
- Thorough testing from the donor to the plasma pool

Plasma product quality begins with the starting material. Collection centres, donors and donations are carefully selected, screened and monitored. Complete information on the source of plasma is an integral part of product registration and, as such, is reported to the national authorities. Each collection center has to be approved by the competent national health authority and has to pass a comprehensive GMP audit by Octapharma.

A guide to plasma sourcing, quality assurance and quality

Octapharma complies with the following directives and guidelines:

- Council of Europe – Guide to the Preparation, Use and Quality Assurance of Blood Components
- European Commission Directives related to blood and plasma
- European Pharmacopoeia – Monograph “Human Plasma For Fractionation”
- CPMP Guidelines (e.g. Plasma Master File, Epidemiology)
- FDA – CFR 21 and current guidelines
- WHO Guidelines

Plasma used to manufacture octanate® is:

- sourced only from countries reported to have a low risk for vCJD
- collected in highly regulated and GMP compliant blood- and plasma collection centres
- tested at state-of-the-art laboratories using validated and approved test systems
- governed by stringent internal and external quality assurance and quality control standards

Octapharma plasma suppliers are:

- authorised by their competent national health authority
- compliant with voluntary IQPP Standards of PPTA (in case of commercial plasmapheresis centers)
- Approved in the European Plasma Master File (PMF) by EMA (European Medicines Agency) if the plasma is to be used for products distributed in the EU
- qualified by Octapharma Quality Assurance Plasma (Audit, Quality Assurance Agreement)
prior to qualification as plasma supplier. At regular intervals, all qualified plasma suppliers are re-audited by Octapharma and are re-inspected by their respective national authorities for compliance.

Each donor has to complete a medical history questionnaire and undergo a physical evaluation prior to donation. Each plasma donation is tested and needs to be non-reactive for antibodies to HCV, HIV-1 and HIV-2, as well as for HBs Antigen. Further, the nucleic acid testing (NAT) is performed on mini-pools for HCV, HIV, HBV, HAV and Parvovirus B19 in compliance with the respective marketing authorisation. Only non-reactive plasma units and pools are used for manufacture of plasma-derivatives.

The donors:
- undergo a basic medical examination prior to each donation
- are thoroughly screened and interviewed by trained personnel and complete a medical history questionnaire
- are assessed for various risk factors (HIV, Hepatitis, vCJD) and are excluded if any such risks are identified
- donors are excluded if they have lived in the UK for longer than six months between 1980 and 1996 or have undergone surgery or received a blood transfusion in the UK

Individual donations are tested with licensed serological test methods for:
- HIV-1 and HIV-2 antibodies, HBs Ag, HCV antibodies, Syphilis. Only non-reactive donations are released for production

Mini-pool donations are tested with NAT (Nucleic Acid Testing) methods for:
- HIV and HCV (100% of the supply), as well as HBV, HAV and Parvovirus B19 (for selected products). Only non-reactive donations are released for production

The Plasma pool:
- is tested for HIV-1 and HIV-2 antibodies and for HBs Ag
- undergoes further NAT testing for HCV as well as HIV, HBV, HAV and Parvovirus B19 in compliance with the respective marketing authorizations. Only non-reactive plasma pools are released for production
Since the middle of the 1980s, the viral safety requirements for plasma-derived products have increased considerably. The manufacturing process for each preparation must ensure (as demonstrated by studies) an adequate capacity for virus elimination. The S/D method sets standards in all respects.

While a number of viral inactivation steps have been shown to greatly enhance the safety of haemophilia products, S/D treatment is the current gold standard for safeguarding plasma-derivatives against the highly infectious lipid enveloped viruses\(^1\). Octapharma was the first manufacturer to employ the S/D method on an industrial scale in the production of plasma-derived biopharmaceuticals. This method has been applied since 1986 for all Octapharma’s coagulation products. The S/D reagents destroy the lipid envelope of viruses. Lipid enveloped viruses, which include the transfusion-relevant, highly infectious viruses HIV, HBV and HCV, are rapidly, effectively and irreversibly destroyed. An infection with HIV, HBV, HCV or other lipid coated viruses has not been found in any patient since

### Requirements for Virus Safety

- Two effective steps against lipid enveloped viruses
- One effective step against non-enveloped viruses
- A combination of methods based on different principles of action
- Inactivation procedures with a high safety margin
- Rapid virus inactivation
- Robustness in the face of process variations
- Validation of each step with a wide variety of viruses
- An individual step efficacy of \(> 4 \log_{10}\)
the introduction of this very robust virus inactivation technology. The viruses used for the octanate® virus validation studies have been carefully chosen in order to cover a wide spectrum of physico-chemical properties and different resistance towards inactivation procedures.

Two effective virus inactivation methods combined

In addition to the S/D method, a terminal dry-heat treatment (TDH) of the final container for 30 minutes at 100°C is applied. The efficacy of this method against lipid enveloped and non-enveloped viruses has been shown for a broad spectrum of viruses. Additional process steps, including precipitation with aluminium hydroxide and ion exchange chromatography contribute to virus safety as well.

With octanate®, Octapharma provides patients with a double virus-inactivated FVIII preparation, which fulfils the latest regulatory requirements for virus safety(2).

Virus validation studies for octanate®(3)

<table>
<thead>
<tr>
<th></th>
<th>Enveloped viruses</th>
<th>Non-enveloped viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model for</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
<td>HAV Hepatitis A Virus</td>
</tr>
<tr>
<td>PRV</td>
<td>Pseudorabies Virus</td>
<td>PPV Porcine Parvovirus</td>
</tr>
<tr>
<td>SBV</td>
<td>Sindbis Virus</td>
<td></td>
</tr>
<tr>
<td>REO</td>
<td>Reovirus</td>
<td></td>
</tr>
<tr>
<td>HAV</td>
<td>Hepatitis A Virus</td>
<td></td>
</tr>
<tr>
<td>PPV</td>
<td>Porcine Parvovirus</td>
<td></td>
</tr>
<tr>
<td><strong>Genome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RNA</td>
<td>DNA</td>
<td>RNA</td>
</tr>
<tr>
<td>RNA</td>
<td>RNA</td>
<td>DNA</td>
</tr>
<tr>
<td><strong>SD treatment [log₁₀]</strong></td>
<td>≥ 5.63</td>
<td>≥ 6.09</td>
</tr>
<tr>
<td><strong>TDH treatment [log₁₀]</strong></td>
<td>4.92</td>
<td>4.55</td>
</tr>
<tr>
<td><strong>Global reduction factor [log₁₀]</strong></td>
<td>≥ 10.55</td>
<td>≥ 10.64</td>
</tr>
</tbody>
</table>

* In a side by side comparison, the TDH used for octanate® has been shown to inactivate B19 faster and by 3 log10 more than PPV due to higher susceptibility of B19 to heat compared to PPV(4.5). In addition, the processing of octanate® resulted in at least 2 log₁₀ B19 reduction(6), which results in a total reduction factor of approximately 8 log₁₀ for B19.
octanate® fulfils all its requirements\(^{(3)}\)

<table>
<thead>
<tr>
<th>Solvent / Detergent Treatment</th>
<th>Terminal Dry Heat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid enveloped viruses</td>
<td>Total reduction</td>
</tr>
<tr>
<td>Two effective steps, each</td>
<td>&gt; 4 log 10</td>
</tr>
<tr>
<td>Non-enveloped viruses</td>
<td>Total reduction</td>
</tr>
<tr>
<td>One effective step</td>
<td>&gt; 4 log 10</td>
</tr>
</tbody>
</table>

3. Data on File-Octapharma internal company report, 2009
5. Mani B et al., Molecular mechanism underlying B19 virus inactivation and comparison to other parvoviruses. Transfusion (2007); 47:1765-1774.
### Manufacturing process for octanate®

<table>
<thead>
<tr>
<th>Process step</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryoprecipitate</td>
<td></td>
</tr>
<tr>
<td>Reconstitution of cryoprecipitate in ethanol and heparin</td>
<td>Reconstitution and stabilisation</td>
</tr>
<tr>
<td>Precipitation with aluminium hydrochloride</td>
<td>Removal of impurities</td>
</tr>
<tr>
<td>Virus inactivation step 1: Solvent/Detergent treatment (0.3% TNBP and 1% Polysorbate 80 for 8 – 12 hours at ±25–26°C)</td>
<td>Inactivation of enveloped viruses</td>
</tr>
<tr>
<td>Ion exchange chromatography</td>
<td>Removal of SD reagents and further purification</td>
</tr>
<tr>
<td>Ultra-diafiltration and concentration</td>
<td>Volume reduction and formulation</td>
</tr>
<tr>
<td>Aseptic filling</td>
<td>Transfer to final container</td>
</tr>
<tr>
<td>Lyophilisation and closure</td>
<td>Removal of water</td>
</tr>
<tr>
<td>Virus inactivation step 2: Terminal Dry Heat treatment of final container (0.6 – 2.0% RM for 31.5 ± 1.5 minutes at +100 ± 1.0°C)</td>
<td>Inactivation of enveloped and non-enveloped viruses</td>
</tr>
<tr>
<td>Quality control and batch release</td>
<td></td>
</tr>
</tbody>
</table>

- **One robust manufacturing process**
- **Two robust viral inactivation steps**
Human FVIII naturally stabilised with VWF

Simply practical and practically simple

Advantages for home treatment

octanate® has a shelf-life of two years when stored at + 2 ºC to + 8 ºC. Convenient packaging allows the separation of the cartons containing the concentrate vial and the solvent (Water for Injections) vial. The concentrate can be stored in the refrigerator while the solvent can be stored separately at room temperature.

octanate® dissolves very quickly. After addition of the water, the concentrate vial only has to be lightly swirled. This greatly reduces the time needed to prepare the concentrate.

Careful and easy record-keeping

According to regulatory recommendations, the application of coagulation products should be documented for every batch so as to allow traceability. Each package of octanate® contains three self-adhesive labels with the batch number. Two labels can be found on the outside of the carton and can simply be pulled off and stuck into records, in order to document dispensing by the physician or pharmacist. The third label on the concentrate vial is used by the patient to record his home treatment. The result is a closed chain of documentation from the manufacturer to the patient, to ensure maximum drug safety.

Haemophilia A Treatment and Prophylaxis

Human FVIII naturally stabilised with VWF
The activity of octanate® is human coagulation factor VIII per vial when reconstituted with 10 ml of Water for Injections.

Further developments for octanate®:

- International post-marketing surveillance NATE-02 has been initiated in April 2010 to evaluate the immunogenicity of octanate® in haemophilia A patients.
- octanate® 1000 in 5 ml is already available in Germany and will be available in other countries soon – as well as octanate® 500 in 5 ml.
- octanate® has already been approved for ITI in Germany and Brazil in patients with FVIII inhibitors and is expected to be approved in other countries in the near future.

Record-Keeping for Treatment Follow-up

The Octapharma Record-Keeping Diary

The patient should have all his information easily accessible, for optimum home treatment follow-up. This includes:

- Reason for treatment (prophylaxis/treatment of bleeding)
- Dosage
- In the event of bleeding: location, severity, duration, assessment of efficacy
- Batch numbers

Precise records facilitate the assessment of treatment. For instance, an increased bleeding frequency or a change in the length of time needed to treat a bleeding episode may indicate that a change of dosage is necessary.

Octapharma has developed a special diary, to help the patient record this information easily, correctly and in an orderly way. All relevant information can be written down here immediately after each injection.

Further Warnings:

Abbreviated Prescribing Information:

octanate® 50 IU/ml (250 IU and 500 IU), Powder and solvent for solution for injection

Composition: octanate® 50 IU/ml contains nominally either 250 IU or 500 IU of human coagulation factor VIII per vial when reconstituted with 5 ml or 10 ml of Water for Injections, respectively. octanate® 100 IU/ml contains nominally 1000 IU of human coagulation factor VIII per vial when reconstituted with 10 ml of Water for Injections. The potency is determined using the European Pharmacopoeia chromogenic assay against the World Health Organization (WHO) International Standard. The mean specific activity of octanate® is ≥ 100 IU/mg of protein.

Therapeutic Indications: Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

Contra-indications: Hypersensitivity to the active substance or to any of the excipients.

Special Warnings and Precautions for Use: The product contains traces of human proteins other than factor VIII. As with any intravenous protein product, allergic-type hypersensitivity reactions are possible, such as hives, generalised urticaria, tightness of the chest, wheezing, hypotension, tachycardia, and may in some cases progress to severe anaphylaxis, including shock. On rare occasions, fever has been observed. Patients with haemophilia A may develop neutralising antibodies to factor VIII which will manifest itself as an insufficient clinical response.

Interaction with Other Medicaments/Other Forms of Interaction: None known.

Pregnancy and Lactation: Because haemophilia A in women is a rare occurrence, experience in the use of factor VIII during pregnancy and breast-feeding is not available. Factor VIII should be used during pregnancy and lactation only if clearly indicated.

Undesirable Effects: Hypersensitivity or allergic reactions, which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, tachycardia, vomiting, wheezing, have been observed infrequently, and may, in some cases, progress to severe anaphylaxis, including shock. On rare occasions, fever has been observed. Patients with haemophilia A may develop neutralising antibodies to factor VIII which will manifest itself as an insufficient clinical response.

In an ongoing clinical trial in previously untreated patients (PUPs), 3 out of 29 (10%) PUPs treated with octanate® on-demand developed inhibitors with a titre above 5 BU. No patients developed inhibitors with a titre below 5 BU. The median number of exposure days at the time of inhibitor detection in these patients was 10 days (range 3-19 days). 26 PUPs had a baseline FVIII activity < 1% and 3 PUPs had < 1% FVIII-C. 28 of 29 PUPs were treated on-demand. During the study, 5 PUPs underwent a surgical procedure. The median age at the first exposure was 9 months (range 3 days to 67 months). The median number of exposure days in the clinical trial was 74 (range 1-553). 20 of 29 patients had more than 20 exposure days.

Excipients: octanate® freeze-dried powder contains: Sodium citrate, sodium chloride, calcium chloride, glycine. octanate® solvent: Water for Injections

Incompatibilities: octanate® must not be mixed with other medicinal products.

Shelf Life: 2 years.

Special Precautions for Storage: Store at + 2°C to + 8°C. Do not freeze. Protect from light.

Prescription only

Marketing Authorisation Holder: Octapharma AG, Seidenstrasse 2, CH 8853 Lachen, Switzerland

Date of Information: May 2009
Octapharma, a Swiss-based company, is an independent, global plasma fractionation specialist. Our core business is the development, production and sale of high quality human proteins. The company has grown to more than 4,000 employees in 28 countries and has introduced sales in more than 80 countries since it was founded in 1983. Octapharma owns five modern, state-of-the-art production facilities in Austria, France, Germany, Sweden and Mexico.

In the highly demanding market of lifesaving plasma products, company success is only possible through reliable product quality and a proven safety record. Over the last six years, in addition to plasma-based activities, Octapharma has dedicated increasing resources to recombinant FVIII expressed in the human cell line. This unique approach is intended to reduce the immunogenic potential and sets Octapharma apart from other companies whose recombinant products are based on animal (murine) cells.

Octapharma respects donated human plasma as a scarce and valuable resource. By using leading edge, validated viral inactivation and purification technologies Octapharma aims to achieve the highest production yields and produce products with the highest possible safety margins.

For more information please visit www.octapharma.com