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4 **Reflection paper on Immune Tolerance Induction in**  
5 **haemophilia A patients with inhibitors**

6 Draft

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11 haemophilia A patients with inhibitors

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## 19 **1. Introduction**

20 In haemophilia A patients, replacement therapy with factor VIII products has become state of the art.  
21 However, a serious complication in the treatment of haemophilia A is the development of neutralizing  
22 antibodies against FVIII, causing therapy resistance and increased risk of bleeding. Up to 30% of  
23 patients with severe haemophilia A develop antibodies against factor VIII treatment. Several factors  
24 (e.g. genetic and environmental) are discussed as possible contributors to inhibitor development. At  
25 present, multiple therapeutic options to overcome the immune response to FVIII concentrates and to  
26 control bleeding situations are implemented in specialised haemophilia centres.

## 27 **2. Discussion**

### 28 *Clinical aspects*

29 Treatment of patients with inhibitory antibodies has to focus on bleeding prevention and inhibitor  
30 eradication:

31 Bleeding prevention might be achieved by high amounts of factor VIII or by bypassing agents such as  
32 recombinant factor VIIa or activated prothrombin complex concentrate.

33 Eradication of the inhibitor might be subject to immune tolerance induction (ITI) or immune-  
34 suppression. Immune tolerance induction involves repetitive higher or lower doses of factor VIII.  
35 Immune-suppression includes chemotherapeutics, corticosteroids and monoclonal antibodies.

36 The immune tolerance induction concept was first reported more than 30 years ago by Brackmann and  
37 Gormsen, Lancet 1977. They showed that high daily doses of factor VIII gradually eliminated the  
38 immune response and the production of anti-FVIII antibodies. The basic principle still applies: repeated  
39 intravenous infusion of factor VIII until inhibitors are no longer detectable and the recovery and half-  
40 life of FVIII are restored. However, up to now, the exact mechanism of immune tolerance induction  
41 remains unclear. Immune tolerance induction has been shown to induce tolerance in most patients  
42 who develop neutralising factor VIII antibodies nevertheless, different treatment protocols and co-  
43 medication options are used. Immune tolerance induction protocols cover high-dose and low-dose  
44 regimens. High-dose protocols recommend the administration of 100-300 IU/kg of factor VIII daily as  
45 one or two doses. Low-dose protocols use 25-50 IU/kg every day or three times/week. Concomitant  
46 treatment with bypassing agents may be used to prevent or treat bleeds.

47 Although several publications are reporting high success rates of about 70% inhibitor eradication  
48 following various immune tolerance induction protocols, those reports reflect heterogeneous data-  
49 collections: Patient inclusion criteria in terms of age, type of inhibitor response, various definitions of  
50 immune tolerance induction success etc. might have an impact on study outcome. Multiple risk factors  
51 have been identified that may affect the success rate of immune tolerance induction, e.g. genetic  
52 factors, treatment history, infections, period between inhibitor occurrence and start of immune  
53 tolerance induction, duration and interruption of immune tolerance induction, and type of factor VIII  
54 product.

55 A similar situation is reflected within Registry data: a high range of individually justified dosages and  
56 therapy durations has been collected. Success of immune tolerance induction depends on the  
57 characteristics of the concerned patient and the experience of the haemophilia centre. All these data  
58 support the assumption that inhibitor eradication is a therapeutic approach that has to be tailored for  
59 the individual patient.

60 The principal results of the International Immune Tolerance Study were published in Blood in 2012.  
61 This prospective, randomized trial in immune tolerance induction comparing high- and low-dose  
62 regimen (200 IU/kg/day versus 50 IU/kg three times per week) was initiated in 2002 and prematurely  
63 closed in late 2009 due to a higher rate of intercurrent bleeding in the low dose arm. Overall success  
64 rates did not differ between the treatment arms. Subjects on high-dose treatment achieved a negative  
65 inhibitor titer and normal FVIII recovery more rapidly than subjects on low dose.

66 Taking the current clinical experience into account, basic scientific aspects remain open. However,  
67 studies on single products cannot be expected to answer the still unsolved general questions, for  
68 example:

- 69 • Are products containing von Willebrand factor more effective than highly purified products for  
70 immune tolerance induction?
- 71 • Is there a difference in efficacy when comparing recombinant and plasma-derived products?
- 72 • Which patients will have a benefit from which immune tolerance induction protocol?
- 73 • Do high or lower dose regimens have a favorable benefit/risk profile for ITI treatment?

74 In summary, the optimal inhibitor eradication strategy has not been established since the management  
75 of neutralizing anti-factor VIII antibodies continues to evolve.

#### 76 ***Regulatory aspects***

77 Historically, many plasma-derived factor VIII concentrates are only authorised nationally. These  
78 products may already have a wording regarding “treatment of inhibitor patients” included in the SmPC.  
79 It could be anticipated that the clinical data base supporting this indication claim might be  
80 heterogeneous and based rather on individual case reports than on GCP compliant clinical trials. It can  
81 be assumed that all plasma-derived and recombinant FVIII products which have a marketing  
82 authorisation and are manufactured by well-known processes are used for immune tolerance induction.  
83 There is no experience so far for the new upcoming products (e.g. modified proteins with long-acting  
84 performance).

85 The previous guidelines on the Clinical Investigation of Human Plasma-Derived/Recombinant Factor  
86 VIII and IX Products stated that “any request for an indication of induction of immune tolerance in  
87 haemophilia A patients with inhibitors should be accompanied by clinical data”. Revision of these  
88 guidelines led to deletion of this statement since the wording was considered vague. It has been  
89 decided that immune tolerance induction in haemophilia A patients with inhibitors should be addressed  
90 in a separate document. Remaining open scientific questions cannot be solved by clinical data provided  
91 for a single product. Clear cut guidance on clinical trials to be performed to endorse an indication claim  
92 for immune tolerance induction cannot be given at present due to the complexity of unresolved  
93 scientific questions, the challenging nature of the management of inhibitor patients, the rarity of the  
94 condition, and the difficulty to undertake controlled trials.

95 However, management of inhibitor patients as well as inclusion of immune tolerance induction  
96 experience with a specific product may be reflected in the SmPC. General guidance regarding  
97 treatment of bleeding episodes and prophylaxis in inhibitor patients is already included in section 4.2  
98 and 4.4 of the core SmPC. It is now proposed that immune tolerance induction experience with a  
99 specific product may be included in section 5.1 of its SmPC with the following statement:

100 “Data on Immune Tolerance Induction (ITI) have been collected in patients with haemophilia A who  
101 have developed inhibitors to FVIII.” This may be followed by a short description of the number of  
102 patients studied, how the data were obtained (e.g. clinical study, registry data), and whether the data

103 show that immune tolerance has been achieved using the product. Success rates from this data, or  
104 information on how immune tolerance was induced should not be included unless this information is  
105 robust as such information may not be meaningful in view of the many variables that can influence the  
106 observed rate.

### 107 **3. Conclusion**

108 Treatment of patients with inhibitory antibodies covers bleeding prevention and inhibitor eradication.  
109 Bleeding prevention might be successfully achieved by high amounts of factor VIII or by bypassing  
110 agents. Eradication of the inhibitor might be subject to several approaches of immune-modulation.

111 Successful eradication of inhibitors in haemophilia patients through immune tolerance induction  
112 remains an individually tailored therapy which has been subject to reports and discussion over the last  
113 30 years. Longstanding clinical experience shows that immune tolerance induction significantly  
114 contributes to therapeutic success. However, commonly agreed eligibility criteria for concerned  
115 patients, treatment regimens regarding dosage and duration as well as success criteria for reproducible  
116 documentation of efficacy have not been developed so far. Therefore, clear cut recommendations on  
117 the clinical trial concept for an individual product in order to achieve an indication claim for immune  
118 tolerance induction cannot be given at present. Clinical research to investigate the key clinical  
119 questions is encouraged and can be supported by European Scientific Advice. In the meantime,  
120 management of inhibitor patients can be reflected in Section 5.1 of the SmPC supported by clinical  
121 data. It can be assumed that there is clinical experience with immune tolerance induction for most of  
122 the plasma-derived and recombinant FVIII products. However, there is no ITI experience with the  
123 long-acting modified products, and therefore, regulatory decision on reflection of immune tolerance  
124 induction in the product information for those products can only be done on a case by case basis.

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