ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. **NAME OF THE MEDICINAL PRODUCT**

Nonafact 100 IU/ml powder and solvent for solution for injection.

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each vial contains nominally 500 IU or 1000 IU of human coagulation factor IX.

Nonafact contains approximately 500 or 1000 IU (100 IU/ml) of human coagulation factor IX after reconstitution.

The potency (IU) is determined using the European Pharmacopoeia one stage clotting test. The specific activity of Nonafact is approximately 200 IU/mg protein.

Produced from the plasma of human donors.

Excipient(s) with known effect:
Sodium chloride

For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Powder and solvent for solution for injection. White powder.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).

4.2 **Posology and method of administration**

Treatment should be under the supervision of a physician experienced in the treatment of haemophilia.

**Previously untreated patients**

The safety and efficacy of Nonafact in previously untreated patients have not been established. No data are available.

**Treatment monitoring**

During the course of treatment, appropriate determination of factor IX levels is advised to guide the dose to be administered and the frequency of repeated infusions. Individual patients may vary in their response to factor IX, demonstrating different half-lives and recoveries. Dose based on bodyweight may require adjustment in underweight or overweight patients. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor IX activity) is indispensable.

**Posology**

The dose and duration of substitution therapy depend on the severity of the factor IX deficiency, on the location and extent of the bleeding and on the patient’s clinical condition.
The number of units of factor IX administered is expressed in International Units (IU), which are related to the current WHO standard for factor IX products. Factor IX activity in plasma is expressed either as a percentage (relative to normal human plasma) or in International Units (relative to an International Standard for factor IX in plasma).

One International Unit (IU) of factor IX activity is equivalent to that quantity of factor IX in one ml of human plasma.

**On demand treatment**
The calculation of the required dose of factor IX is based on the empirical finding that 1 International Unit (IU) factor IX per kg body weight raises the plasma factor IX activity by 1.1 % of normal activity. The required dose is determined using the following formula:

\[
\text{Required units} = \text{body weight (kg)} \times \text{desired factor IX rise (%) (IU/dl)} \times 0.9
\]

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.

In the case of the following haemorrhagic events, the factor IX activity should not fall below the given plasma activity level (in % of normal or IU/dl) in the corresponding period. The following table can be used to guide dosing in bleeding episodes and surgery:

<table>
<thead>
<tr>
<th>Degree of haemorrhage / Type of surgical procedure</th>
<th>Factor IX level required (%) (IU/dl)</th>
<th>Frequency of doses (hours)/Duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding</td>
<td>20-40</td>
<td>Repeat infusion every 24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma</td>
<td>30-60</td>
<td>Repeat infusion every 24 hours for 3-4 days or more until pain and acute disability are resolved.</td>
</tr>
<tr>
<td>Life threatening haemorrhages</td>
<td>60-100</td>
<td>Repeat infusion every 8 to 24 hours until threat is resolved.</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor surgery including tooth extraction</td>
<td>30-60</td>
<td>Every 24 hours, at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>Major surgery</td>
<td>80-100 (pre- and postoperative)</td>
<td>Repeat infusion every 8-24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor IX activity of 30 % to 60 % (IU/dl).</td>
</tr>
</tbody>
</table>

**Prophylaxis**
For long-term prophylaxis against bleeding in patients with severe haemophilia B, the usual doses are 20 to 40 IU of factor IX per kilogram of body weight at intervals of 3 to 4 days.
In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

**Paediatric population**
The safety and efficacy of Nonafact in children 0 to 6 years of age have not been established. No data are available.

**Method of administration**
Intravenous use. It is recommended that the rate of administration should not exceed 2 ml/min.

For instructions on reconstitution of the medicinal product before administration, see section 6.

**4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Known allergic reaction to mouse protein.

**4.4 Special warnings and precautions for use**

**Hypersensitivity**
Allergic type hypersensitivity reactions are possible with Nonafact. The product contains traces of mouse proteins. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the product immediately and contact their physician.

Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

In case of shock, standard medical treatment for shock should be implemented.

**Inhibitors**
After repeated treatment with human coagulation factor IX products, patients should be monitored for the development of neutralising antibodies (inhibitors) that should be quantified in Bethesda Units (BU) using appropriate biological testing.

There have been reports in the literature showing a correlation between the occurrence of a factor IX inhibitor and allergic reactions. Therefore, patients experiencing allergic reactions should be evaluated for the presence of an inhibitor. It should be noted that patients with factor IX inhibitors may be at an increased risk of anaphylaxis with subsequent challenge with factor IX.

Because of the risk of allergic reactions with factor IX products, the initial administrations of factor IX should, according to the treating physician’s judgement, be performed under medical observation where proper medical care for allergic reactions could be provided.

**Thromboembolism**
Because of the potential risk of thrombotic complications, clinical surveillance for early signs of thrombotic and consumptive coagulopathy should be initiated with appropriate biological testing when administering this product to patients with liver disease, to patients post-operatively, to new-born infants, or to patients at risk of thrombotic phenomena or DIC. In each of these situations, the benefit of treatment with Nonafact should be weighed against the risk of these complications.

**Cardiovascular events**
In patients with existing cardiovascular risk factors, substitution therapy with FIX may increase the cardiovascular risk.

**Catheter-related complications**
If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteremia and catheter site thrombosis should be considered.
Viral safety
Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses or other pathogens.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), and for the non-enveloped viruses such as hepatitis A and parvovirus B19.

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of plasma-derived factor IX products.

It is strongly recommended that every time that Nonafact is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium-free’.

Paediatric population
The listed warnings and precautions apply both to adults and children.

4.5Interaction with other medicinal products and other forms of interaction
No interactions of human coagulation factor IX products with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation
Animal reproduction studies have not been conducted with factor IX. Based on the rare occurrence of haemophilia B in women, experience regarding the use of factor IX during pregnancy and breast-feeding is not available. Therefore, factor IX should be used during pregnancy and lactation only if clearly indicated.

4.7 Effects on ability to drive and use machines
Nonafact has no influence on the ability to drive and use machines.

4.8 Undesirable effects
Summary of the safety profile
Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed rarely and may in some cases progress to severe anaphylaxis (including shock). In some cases, these reactions have progressed to severe anaphylaxis, and they have occurred in close temporal association with development of factor IX inhibitors (see also 4.4). Nephrotic syndrome has been reported following attempted immune tolerance induction on haemophilia B patients with factor IX inhibitors and a history of allergic reaction.
Nonafact contains trace amounts (< 0.1 ng mouse IgG/IU of factor IX) of the murine monoclonal antibody used in its purification. In theory, therefore, the use of Nonafact could generate antibodies to mouse protein. The clinical relevance of antibodies to mouse protein, if these do indeed arise, is not known.

Patients with haemophilia B may develop neutralising antibodies (inhibitors) to factor IX. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

There is a potential risk of thromboembolic episodes following the administration of factor IX products, with a higher risk for low purity preparations. The use of low purity factor IX products has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. The use of high purity factor IX is rarely associated with such adverse reactions.

For safety information with respect to transmissible agents, see 4.4.

Tabulated list of adverse reactions
The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data)

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness

<table>
<thead>
<tr>
<th>MedDRA system organ class (SOC)</th>
<th>Adverse reaction (PT)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Anaphylactic reaction</td>
<td>Not known</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>Not known</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Pyrexia</td>
<td>Not known</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Flushing</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Description of selected adverse reactions
The adverse reaction flushing is reported in a clinical trial. The other (serious and non-serious) adverse reactions were received by spontaneous reporting.

Paediatric population
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via ‘het Nederlands Bijwerkingen Centrum Lareb (Website: www.lareb.nl)’.

4.9 Overdose
No symptoms of overdose with human coagulation factor IX have been reported.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihemorrhagics, blood coagulation factor IX. ATC code: B02BD04.

Factor IX is a single chain glycoprotein with a molecular mass of about 68,000 Dalton. It is a vitamin K-dependent coagulation factor and is synthesised in the liver. Factor IX is activated by factor Xla in the intrinsic coagulation pathway and by the factor VII/tissue factor complex in the extrinsic pathway. Activated factor IX, in combination with activated factor VIII, activates factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot is formed. Haemophilia B is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor IX and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma level of factor IX is increased, thereby enabling a temporary correction of the factor IX deficiency and correction of the bleeding tendencies.

Paediatric population
There are insufficient data to recommend the use of Nonafact in children less than 6 years of age.

5.2 Pharmacokinetic properties

The \textit{in vivo} increase in factor IX levels obtained with Nonafact is 1.1 IU/dl per IU administered per kg body weight, which corresponds to an \textit{in vivo} recovery of 49\%. Nonafact has a half-life of approximately 19 (17 – 21) hours.

5.3 Preclinical safety data

Plasma coagulation factor IX is a normal constituent of human plasma. Factor IX in this product therefore behaves like endogenous factor IX. Conventional animal toxicity studies and mutagenicity studies with plasma coagulation factor IX were not carried out. In pharmacodynamic studies in rabbits and guinea pigs, the thrombogenicity of Nonafact was shown to be minimal.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Sodium chloride
Sucrose
Histidine.

Solvent:
Water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

After reconstitution:
Chemical and physical in-use stability has been demonstrated for 3 hours at a temperature of 21°C.
From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (at 2°C – 8°C). Do not freeze. Keep the vials in the outer carton, in order to protect from light. For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

500 IU: one vial (glass type I) of powder + one vial (glass type I) of 5 ml solvent with stoppers (bromobutyl).

1000 IU: one vial (glass type I) of powder + one vial (glass type I) of 10 ml solvent with stoppers (bromobutyl).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution

1. Bring the two vials to a temperature between 15°C and 25°C.
2. Remove the plastic cap from the vials.
3. Disinfect the surface of the stoppers of both vials with a gauze soaked in 70 % alcohol.
4. Remove the protective sheath from one end of a transfer needle and pierce the stopper of the vial containing water for injections. Remove the protective sheath from the other end of the transfer needle. Invert the solvent vial and pierce the stopper of the vial containing the powder.
5. Tilt the product vial when transferring the solvent to allow the solvent to flow down the side of the vial.
6. Remove the empty vial and the transfer needle.
7. Swirl the vial gently to completely dissolve the powder within 5 minutes. The resulting solution is clear, colourless to light yellow and has a neutral pH.

Reconstituted products should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanquin Plasma Products B.V.
Plesmanlaan 125
NL-1066 CX Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/186/001 (500 IU)
EU/1/01/186/002 (1000 IU)
9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 03 July 2001
Renewal of authorisation: 03 July 2006

10. DATE OF REVISION OF TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMA) [http://www.ema.europa.eu](http://www.ema.europa.eu).

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