

## SCIENTIFIC DISCUSSION

**This module reflects the initial scientific discussion for the approval of NovoSeven. This scientific discussion has been updated until 1 February 2004. For scientific information on procedures after this date please refer to module 8B.**

### 1. Introduction

NovoSeven is a novel product and contains activated recombinant DNA human coagulation factor VII (rFVIIa).

The recombinant molecule is produced in baby hamster kidney (BHK) cells.

Recombinant FVIIa is almost identical to human plasma FVIIa except for a difference in glycosylation. This difference is not expected to be of relevance.

Factor VII is a blood clotting protein that participates in the coagulation process leading to formation of a fibrin clot. The apparent mechanism of action of NovoSeven (rFVIIa) is activation of the final common pathway of the coagulation cascade independent of the presence of factor VIII and factor IX. rFVIIa forms a complex with tissue factor, which in the presence of calcium and phospholipids activates coagulation factor X which then initiates the conversion of prothrombin into thrombin.

The following indications were initially claimed: "Serious bleeding events and surgery in patients with inhibitors to coagulation Factor VIII or Factor IX." At a later stage the Summary of Product Characteristics has been revised to include that in certain circumstances the product could be administered at home. However the MAH submitted data to support 2 new indications, these are: Two additional indications (Treatment of bleeding episodes and prevention of bleeding in those undertaking surgery or invasive procedures in patients with congenital FVII deficiency and in patients with Glanzmann's thrombasthenia with antibodies to GP IIb-IIIa and/or HLA and with past or present refractoriness to platelet transfusions) which received positive opinion by the CPMP in October 2003.

Pharmacodynamic, pharmacokinetic and toxicological studies were submitted as well as clinical studies.

### 2. Chemical, pharmaceutical and biological aspects

NovoSeven is a lyophilised preparation of recombinant DNA human coagulation factor VIIa (rFVIIa). It is a 50 kD glycoprotein processed by a genetically transformed mammalian cell line (BHK, Baby Hamster Kidney) and purified by *consecutive chromatography steps, including* immunoaffinity chromatography using murine monoclonal antibodies. FVII is translated as a single chain protein (406 AA), which during purification is converted into the two chains, activated form.

To ensure a rFVIIa shelf life of at least two years, it was necessary to formulate rFVIIa as a freeze dried product. Apart from the rFVIIa, the composition consists of five excipients all necessary in order to achieve a stable lyophilised formulation, which is easy to reconstitute and which is isotonic. The excipients are: Sodium chloride, calcium chloride dihydrate, glycyglycine, polysorbate 80, mannitol.

Glycyglycine was chosen as the buffer substance because it has the following characteristics:

1. Seen from a chemical point of view glycyglycine is the simplest dipeptide and toxicological studies have shown that it has no effect at the concentration used.
2. Glycyglycine has a suitable buffer capacity in the rFVIIa bulk and the finished product.
3. Glycyglycine is fully compatible with rFVIIa and calcium.

NovoSeven is presented in glass vials containing 1.2 mg, 2.4 mg resp. 4.8 mg lyophilised rFVIIa.

#### Impurities

The rFVIIa purification process has proven to be efficient for removal of the potential impurities arrived from the cell culture or introduced during the purification process.

For impurities, that were not detectable in the bulk product by the available methods, validation of each purification step of the process, performed either in full production scale or in model systems, gave evidence for the removal of the impurities.

### **Fermentation and production process**

The production runs take place in a fermentor. Cells from one ampoule of the MWCB are used for the initiation of each production run. The cells are propagated into sufficient amounts before inoculation of the production fermentor. The fermenters are conventional stirred tanks. Every 24 hours part of the culture liquid is harvested and replaced by new medium. A serum containing medium is used for the production phase.

During development and clinical trial phase changes have been made in scale of the fermentation of the active ingredient. Early clinical trials have been performed using bulk product from a pilot plant scale. Later trials were performed with the bulk product produced in full scale.

### **Viral contamination**

Occasionally virus contamination occurs during the fermentation and most likely it originates from the bovine serum. However, all detected viruses are considered to be no pathogenic to humans.

Contaminated harvests are rejected for production of NovoSeven. In order to prevent cross-contamination through the fermentation and purification process adequate measures have been taken.

The purification is validated for a wide range of model and relevant viruses (RNA and DNA viruses, enveloped and non-enveloped viruses).

All studies have been performed in compliance with the CPMP Notes for Guidance.

The company committed to reviewing their production strategy in order to reduce the risk of viral contamination associated with the use of several batches of New-born Calf Serum in the same campaign.

The CPMP considered that the procedures put in place by the company to ensure the viral safety of the finished product are reassuring and that it is very unlikely that a virus contaminated batch of the finished product will be released.

The company committed to continuing their effort to identify those serum batches which are a source of the virus.

## **INSPECTION STATUS**

The Applicant requested the following manufacturing sites to be considered:

### **Manufacturer of the active substance:**

Novo-Nordisk A/S Hallas Alle  
DK-4400 Kalundborg, Denmark

### **Manufacturer and storage of the finished medicinal product:**

Novo Nordisk A/S Hagedornsvej  
DK-2820 Gentofte Denmark

### **Manufacturer responsible for batch release**

Novo Nordisk A/S Hagedornsvej  
DK-2820 Gentofte Denmark

Manufacturing authorisation was released to Novo Nordisk A/S Denmark for these three sites from the National Board of Health (SUNDHEDSSTYRELSEN) on 21 November 1994.

### 3. Toxicopharmacological aspects

Recombinant factor VIIa (rFVIIa) is a human coagulation factor of the family of the vitamin K dependent coagulation factors. It is a glycoprotein consisting of 406 amino acid residues.

In the presence of calcium and phospholipids, factor VII/VIIa in a complex with tissue factor can activate factor X to factor Xa directly, bypassing factor IX or factor VIII. Activation of factor X to factor Xa initiates the common pathway of the coagulation cascade where prothrombin is activated to thrombin, which converts fibrinogen to fibrin.

#### Pharmacodynamics

rFVIIa induced haemostasis in dogs with hemophilia A and B as well as in Warfarin-treated rats.

rFVIIa showed a local pharmacological effect at the site of the induced lesion. No systemic activation of the coagulation cascade was demonstrated, except at high doses.

Safety pharmacology was studied extensively. There were no clinically relevant findings.

#### Pharmacokinetics

The volume of distribution is somewhat larger than the blood volume, rFVIIa is rapidly cleared from the plasma in the rat ( $t^{1/2}$  roughly 0.5 h), whereas in larger animals (dog, monkey) and in humans  $t^{1/2}$  is about 3 h. In most animals human rFVIIa is stable in plasma, in the rabbit, however, it is not.

Apart from differences in plasma clearance the fate of human rFVIIa in humans and in laboratory animal species is similar.

#### Toxicology

The toxicological profile of NovoSeven was studied very extensively.

In acute studies in mice the lungs were affected (intravascular coagulation). No coagulated blood was seen in rat pulmonary arteries.

Four week and 13 week repeated dose i.v. studies were performed in rats and Cynomolgus monkeys.

In rats the main effects were increased thrombus formation and irritation at the injection site (bolus injection) and thromboembolism in the pulmonary circulation (1.1 mg/kg/day).

In monkeys doses up to 3 mg/kg/day for 13 weeks were tolerated well except for minor local reactions at the injection site and minor thromboemboli in the lungs.

No general activation of the coagulation system was observed in the toxicity studies as measured by fibrinogen, antithrombin III or  $\alpha_2$  antiplasmin.

Time-dependent antibody development was seen in rats, but no hyper-sensitivity nor immunological tissue damage was seen. In monkeys, antibody formation was dose and time dependent (as in rats) and the cross-reacting antibodies measured, had a neutralising effect on rFVIIa, thus resulting in prolonged prothrombin times.

- Dogs developed an immunological response to treatment with this human protein and this species is unsuitable for repeated dose studies.
- A fertility and general reproductive performance study in rats (up to 3 mg/kg/day) did not reveal adverse effects except for local reactions at the injection site.
- No embryotoxicity studies are performed.
- Mutagenicity tests are not relevant in view of the proteinaceous nature of the test compound. Nevertheless, a clastogenicity test (in vitro) in human lymphocytes and a micronucleus test (in vivo) have been conducted both with negative outcome.
- Carcinogenicity studies were not considered necessary for this product.
- In special studies on antigenicity no specific antibody formation against BHK cell protein was shown.

A number of studies with the inactive ingredient glycylglycine, the dipeptide of the non-essential amino acid glycine, were submitted: acute studies, repeated dose studies (up to 12 months), a segment 1 reproduction study, and mutagenicity studies. Glycylglycine was not toxic (except for a slight effect on the intestinal transit rate: see “pharmacodynamics”) and not mutagenic. The Observed Adverse Effect Level of glycylglycine (166 mg/kg in rats and > 640 mg/kg in dogs) is far higher than the maximal therapeutic exposure of ca 2.5 mg/kg/day.

In conclusion the pharmaco-toxicological dossier submitted was considered adequate to describe and assess the pharmaco-toxicological potential of eptacog alfa (activated).

#### **4. Clinical aspects**

Factor VII is a blood clotting protein that participates in the coagulation process leading to formation of a fibrin clot. The apparent mechanism of action of NovoSeven (rFVIIa) is activation of the final common pathway of the coagulation cascade independent of the presence of factor VIII and factor IX.

rFVIIa forms a complex with tissue factor, which in the presence of calcium and phospholipids activates coagulation factor X which then initiates the conversion of prothrombin into thrombin.

Pharmacokinetic studies were submitted as well as a clinical studies.

As the initial claimed indication was “Serious bleeding events and surgery in patients with inhibitors to coagulation factor VIII or factor IX” general aspects concerning the current available treatments of patients with inhibitors were taken into consideration. Two additional indications (Treatment of bleeding episodes and prevention of bleeding in those undertaking surgery or invasive procedures in patients with congenital FVII deficiency and in patients with Glanzmann’s thrombasthenia with antibodies to GP IIb-IIIa and/or HLA and with past or present refractoriness to platelet transfusions) received positive opinion by the CPMP in October 2003.

Approximately 3.6% to 25% of individuals with haemophilia A develop inhibitors to factor VIII. The incidence of antibodies is higher in patients with severe haemophilia (factor VIII < 1-2%) than in patients with moderately severe or mild haemophilia A. In haemophilia B patients, a much rarer disease than haemophilia A, the incidence of inhibitors is much lower (around 5%).

Treatment of bleeding episodes in haemophilic patients with factor VIII inhibitors has to be individually tailored, depending on the type and the titer of the antibodies.

Patients with low level inhibitors (<10 BU) often respond to repeated infusion of factor VIII concentrate with a rise in plasma factor VIII. Treatment of all bleeding episodes with factor VIII may eventually lead to a decline in the antibody level during a few days.

In order to achieve haemostasis in high responder patients and/or patients with a titer > 10 BU, other therapeutic approaches are mandatory, such as bypassing the FVIII coagulation pathway.

A variation type II/31 was submitted by the MAH to change the cut-off inhibition titer from > 10 BU to > 5 BU. The International Society of Thrombosis and Haemostasis (ISTH) reviewed a large number of treatment cases to determine the efficacy of regimens, products used and treatment outcomes. Based on this, the cut-off limit > 5 BU/ml was recommended. To be in compliance with these guidelines the limit in the NovoSeven SPC has been changed from > 10 BU/ml to the recommended > 5 BU/ml.

#### **Pharmacodynamics**

A total number of 27 patients were studied.

Out of 27 patients 26 had haemophilia A, and 1 haemophilia B.

Out of 27 patients 15 had inhibitors against factor VIII, 11 (all haemophilia A) had no inhibitors.

In 23 occasions rFVIIa was given in association with a bleed and 32 administrations in patients without an ongoing bleed.

The FVII:C levels in plasma increased in a dose dependent way. Pre-treatment prothrombin time (PT) was normal (10-13 sec) in all subjects and shortened between 2.2 and 2.8 sec following the

administration of rFVIIa. No further shortening of the PT occurred with plasma FVII:C > 4-5 U/ml.

APTT was prolonged in all patients prior to treatment and shortened after rFVIIa administration. Factor X level was increased linearly with dose in 31 non-bleeding and 18 bleeding episodes.

Factor IX levels in plasma at 20 minutes after rFVIIa administration increased in 24 out of 32 observations.

No dependence was observed between factor IX level and the rFVIIa dose.

The clinical effect paralleled increasing plasma-FVII:C levels (mean 17.1 U/ml, range 13.2-21.9) at 70 µg/kg dose level.

### **Pharmacokinetics/pharmacodynamics**

Not all 27 patients treated with rFVIIa in these studies had inhibitors to factor VIII (15/26) or factor IX. Increases in FVII:C levels as well as the AUC after administration of rFVIIa were dose dependent. No difference was found between the two rFVIIa preparations prepared in Pilot Plan and Large Scale preparations.

It is difficult to interpret the pharmacokinetic data in terms of relation with clinical effect of rFVIIa ; this is not of primary importance in judging efficacy of rFVIIa, as it is not known what plasma-level of FVIIa is necessary to achieve an initial haemostasis or to maintain a functional haemostasis in patients lacking the FVIII/IX dependent enforcement loop.

Furthermore rFVIIa is supposed not to induce any systemic activation of the coagulation cascade as the product forms complex with tissue factor (in the presence of phospholipids and calcium) exposed locally at the site of injury. rFVIIa is not proteolytically active by itself.

There are no reliable suitable laboratory markers available for measuring the efficacy of rFVIIa.

Clinical data should be the most important endpoint of efficacy.

Nevertheless, on a theoretical basis monitoring of PT levels and recovery of FVIIa are useful in the situation when there is no clinical response.

### **Safety profile**

For all patients treated with rFVIIa in various studies in a time period of 4 years a total of 23 serious adverse events and 115 non serious adverse events have been reported. The figures represent the treatment of a total of 722 bleeding episodes and 88 non bleeding episodes (230 patients).

Twenty four (21%) of the events were related to the body system as a whole. The majority of the events were, apart from two cases of allergic reactions, fever and malaise (all of mild to moderate severity).

The two allergic reaction, reported in the same patients were considered probably related to the study drug. In 14 (12%) of the cases the events were related to the gastrointestinal system (12/114 nausea and vomiting).

Skin and appendages were involved in 13% (14 events).

Platelet, bleeding and clotting disorders were reported in 9% of the cases (10 events).

For the non serious adverse events, 9 events were probably related to the study drug, 42 events possible related, 52 events unlikely related and 2 probably not related and 10 impossible to assess.

There was no correlation between dose of factor VIIa and occurrence of non-serious adverse events.

Two events resulting in death as the outcome were considered possible related to rFVIIa: one patient went into circulatory shock caused by a gastrointestinal bleeding 3 days after initiation of rFVIIa; A second other patient developed acute renal failure after treatment with rFVIIa for a surgical bleed and was retreated 8 days later for a minor surgical procedure still experiencing acute renal failure. Thirteen days later the patient aspirated stomach contents and died 1 day later (aspiration pneumonia, brain stem infarct and haemophilia).

In two studies laboratory parameters for intravascular coagulation were assessed and found to be normal. In one patient there was laboratory evidence of consumption coagulopathy.

A warning on the possible thrombogenic potential for all patients treated with NovoSeven was included in the Summary of Product Characteristics.

### **Antigenicity of rFVIIa**

In three clinical trials specific antibody formation has been followed in a total of 137 patients (119 haemophilia A, 7 haemophilia B and 2 FVII deficient patients and 9 non-haemophiliacs with acquired inhibitors. Four patients had elevated levels in the FVII:Ab assay before rFVIIa treatment (in one patient considered to be falsely positive, in three other patients there was no increased response in relation to treatment). In only 2 “FVII deficient patients” antibody formation was tested after treatment with rFVIIa. One of these two patients developed antibodies to rFVIIa after mistakenly receiving an overdose of rFVIIa. A total of 72 patients who received rFVIIa in three clinical trials have been followed for specific antibody formation. Human antibodies to FVIIa have not been detected, neither before nor after treatment with rFVIIa. Likewise, no antibody formation against potential contaminants has been demonstrated.

### **Overall comments on the clinical data**

In summary, the submitted data gave sufficient evidence that rFVIIa is effective and safe with regard to treatment of bleeding episodes in patients with factor VIII/IX inhibitors, as demonstrated by the fact that in the largest submitted study (IV B 1.01-01) including 61 haemophilia (A and B) patients, the overall efficacy rate was 84% for 57 serious bleeds treated and 59% for 38 surgical bleeds treated with rFVIIa.

No development of antibodies against FVIIa in 72 patients tested was detected.

Only 3 patients with haemophilia B inhibitors were treated with rFVIIa for serious bleeds or surgical procedures (in study IV B. 01.01): effect of rFVIIa in these patients is likely from the apparent mechanism of action of rFVIIa. However, since these patients are extremely rare a request for significantly more patients seems not to be realistic.

With respect to safety, the data of rFVIIa submitted so far suggest that the thrombogenic potential is low.

Nevertheless rFVIIa may have the potential to induce disseminated intravascular coagulation (DIC) in clinical situations with increased tissue factor in circulating blood (one patient did develop DIC and died).

In total, two cases of disseminated intravascular coagulation (DIC) have been described that were related to rFVIIa administration. Other thromboembolic events have not been associated with rFVIIa injections.

With regard to the occurrence of viral infections, the risk of transmissions of viral infections is likely to be low.

On the basis of the data provided, all references to factor VII deficiency were deleted from the first submitted Summary of Product Characteristics. A warning on the possible thrombogenic potential for all patients treated with NovoSeven was included in the Summary of Product Characteristics.

After the granting of the Authorisation of NovoSeven the MAH submitted a variation application with the results of an open-label phase III study “to evaluate the safety and efficacy of rFVIIa when administered in the home to control joint, muscle and mucocutaneous bleeds in haemophiliacs with inhibitors”. The company with data supporting submitted an expert report that rFVIIa is a safe and effective treatment in the home setting. In the submitted study 60 patients with inhibitors to FVIII (92% had haemophilia A) or FIX (although not all patients had high titer inhibitors at the time of inclusion) were treated for mild or moderate bleeding episodes with NovoSeven at home under careful instructions by the haemophilia nurse.

The results of the study show that in a patient group with mild to moderate bleeding episodes, NovoSeven given at home can achieve effective haemostasis in about 90% of bleeding episodes. Side effects are acceptable. The CPMP concluded that the greatest benefits of home therapy to the patients are savings in time lost due to earlier treatment of the bleeding episode. Due to the short half-life of

the product the approach of home treatment at 3 hour intervals offers logistic advantages over in hospital treatment. With respect to home treatment a statement was added in the Summary of Product Characteristics that this does not concern serious bleeding episodes and that, in the case of mild or moderate bleeding episodes, administration of NovoSeven should only be done in close collaboration with a haemophilia centre where the patient is regularly followed up.

## **5. Overall conclusions and benefit/risk assessment**

Although the clinical data submitted were limited, activated recombinant DNA coagulation factor VII (rFVIIa) gave evidence to be effective in the treatment of haemophilia patients with inhibitors. The efficacy data showed 84% good response in 57 surgical bleeds and 59% response in 38 surgical bleeds [compassionate need study (IV B. 1-01.01)] in 61 “bad risk” patients with inhibitors. In these patients alternative treatment would likely prove ineffective for coverage of surgery in cases where the patients experienced a life - or limb threatening bleed. With respect to safety, the data of rFVIIa submitted so far suggest that the thrombogenic potential is low.

During the centralised procedure, questions regarding the preclinical issues were answered comprehensively so that no issues were left open.

The CPMP considered that the procedures put in place by the company to ensure the viral safety of the finished product were reassuring and that it is very unlikely that a virus contaminated batch of the finished product will be released.

Thus a favourable opinion for granting a marketing authorisation was issued on 23 February 1996.

On 4 December 1997, following the submission of a variation type II, the Commission granted an amended Marketing authorisation for NovoSeven. As result of this variation, NovoSeven can be administered to patients at home under close monitoring. The new therapeutic indication granted is treatment of bleeding episodes and surgery in patients with inherited or acquired haemophilia with inhibitors to coagulation factors (FVIII or FIX) > 10 BU or in patients with antibody titer < 10 BU who are expected to have a high anamnestic response to factor VIII or factor IX.

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of NovoSeven was favourable in the treatment of bleeding episodes and prevention of excessive bleeding in connection with surgery in patients with inherited or acquired haemophilia with inhibitors to coagulation factors (FVIII or FIX).

## **6. Extension of the indication in patients with Glanzmann’s thrombasthenia with antibodies to GP IIb- IIIa and/or HLA, and with past or present refractoriness to platelet transfusions.**

Glanzmann’s thrombasthenia (GT) is a rare autosomal recessive disorder of platelet function. In most cases there is a quantitative deficiency of the GP IIb-IIIa receptor on the platelet. In a small number of patients the quantity of receptor is normal but it has an abnormal sequence and is ineffective.

GP IIb-IIIa receptors bind fibrinogen and other adhesive proteins. In GT the platelets cannot aggregate and a defective platelet haemostatic plug is formed. Patients with GT present with purpura, a normal platelet count, a long bleeding time and abnormal platelet aggregation to ADP and associated agonists with normal ristocetin aggregation.

NovoSeven is an activated factor VII molecule currently licensed for the treatment of haemophiliacs with antibodies to factor VIII and factor IX. There is a good biological plausibility for this use, since factor VIIa is the product of the extrinsic pathway and can activate factor IX and factor X bypassing the need for factor VIII and generating thrombin thus forming a clot.

All of these mechanisms are intact in patients with Glanzmann’s thrombasthenia, however it is postulated that a large bolus dose of factor VIIa generates a large amount of thrombin, which sets off a feedback loop activating the intrinsic pathway. There is some animal evidence to suggest that

pharmacological doses of factor VIIa directly activate factor X on the surface of the platelets independent of tissue factor. A clear pharmacological rationale for the use of NovoSeven in this indication however is not available.

Results of in vitro models support the haemostatic effect of rFVIIa in Glanzmann's thrombasthenia. In a perfusion chamber model using reconstituted blood, platelets deficient in GP IIb/IIIa, extra-cellular matrix of stimulated human umbilical vein endothelial cells and collagen type III, it was found that rFVIIa increased thrombin generation and significantly increased adhesion of these defective platelets to the sub-endothelial structure.

Upon vascular injury, platelets adhere to exposed sub-endothelium and become activated.

Recombinant FVIIa binds to activate platelets and converts factor X to factor Xa (in vitro data). The ability of pharmacological doses of rFVIIa to increase thrombin generation locally at the site of vascular injury may compensate for the defects in platelets in patients with Glanzmann's thrombasthenia via the formation and polymerisation of fibrin as well as the activation of factor XIII to factor XIIIa.

Platelet transfusion is the current standard treatment of Glanzmann's thrombasthenia when local measures or anti-fibrinolytic drugs fail to stop bleeding or during invasive/surgical bleeding. Potential complications of platelet transfusions are allo-immunisation to HLA or GP IIb/IIIa, rendering future platelet transfusions ineffective, and the transmission of viral or bacterial infection.

The clinical experience with the treatment of patients with Glanzmann's thrombasthenia with rFVIIa is based on the data from a clinical trial, the International Registry on Recombinant Factor VIIa and Congenital Platelet Disorders, and published case reports. As the four patients in the clinical trial were also included in the International Registry as well as six out of 10 published case reports, there is considerable overlap in the discussion of the data.

The inclusion criteria in the clinical trial did not comprise the existence of anti-GPIIb/IIIa and/or anti-HLA antibodies, nor refractoriness to platelet transfusions. Only one of the four children in the clinical trial matched the requested therapeutic indication: this patient had anti-GPIIb/IIIa antibodies and was refractory to platelet transfusions. All 18, predominantly mucosal, bleeding episodes in this patient stopped, 13 within 24 hours after the first rFVIIa dose and three after 24 hours. In three episodes the time to stop the bleeding was not recorded but the treating physician recorded two of the three cases as a success. In two other patients the efficacy of rFVIIa cannot be evaluated. Both patients received only one dose of rFVIIa with a concomitant platelet transfusion. The fourth patient did not match the requested indication: in this patient a surgical procedure was carried out successfully under the cover of rFVIIa. No adverse events were reported in the clinical trial.

In the International Registry 59 patients were treated with rFVIIa for 108 bleeding episodes and 34 invasive/surgical procedures. Treatment with rFVIIa was successful (bleeding stopped and no recurrence) in 58% (7/12) of the GI bleeds, 67% (28/42) of the nosebleeds, and 72% (21/29) of the oropharyngeal bleeds. All 9 dental extractions were performed successfully. In the 7 evaluable cases of major surgery, success was recorded in 6 procedures. Fourteen of the 15 evaluable minor invasive/surgical procedures were performed successfully.

In the account of efficacy of rFVIIa per type of bleeding episode or per type of invasive/surgical procedure, no discrimination has been made between episodes or procedures occurring in patients with or without anti-GPIIb/IIIa and/or anti-HLA antibodies and with or without refractoriness to platelets. Overall, of the 57 evaluable bleeds in patients with platelet antibodies or platelet refractoriness, 42 were successfully treated (74%), 4 recurred (7%) and treatment failed in 11 (19%). Among the 40 evaluable episodes in patients without platelet refractoriness and antibodies, 28 were successfully treated (70%), 3 recurred (7%) and treatment failed in 9 (23%). The CPMP requested that the efficacy data of the International Registry and the four independently published case reports should be analysed separately for patients with anti-GPIIb/IIIa and/or anti-HLA antibodies and platelet refractoriness. MAH has performed this additional analysis and the results have shown that the number of evaluable surgical/invasive procedures and bleeding episodes dropped considerably compared with the original application. The present re-analysis is based on 17 patients from the International Registry and two patients from independently published case reports. The data



demonstrate that rFVIIa was effective for bleeding prophylaxis in 18 (95%) of 19 evaluable (minor plus major) surgical procedures. rFVIIa was effective in stopping 28/40 (70%) of the evaluable bleeding episodes, which is similar as the efficacy in bleeding episodes recorded in the original report. Three recurrent bleedings (3/40, 8%) could be successfully treated with additional doses of rFVIIa (but in one case a concomitant platelet transfusion was given).

From January 1995 to February 2003 there were 10 published case reports on the use of rFVIIa in Glanzmann's thrombasthenia. Six case reports were included in the International Registry. Four cases were published independently. Among the 10 cases published, rFVIIa was used in 9 bleeding episodes and 5 invasive/surgical procedures. Haemostasis was achieved in 6 out of 9 bleeding episodes and in all 5 surgical/invasive procedures. Seven patients had platelet refractoriness or anti-platelet antibodies but it is not clear from the submitted data what the outcome of treatment with rFVIIa was in these patients.

The CPMP requested additional data on safety and efficacy of the proposed dosage regimen. Based on published data on the use of rFVIIa in Glanzmann's thrombasthenia, a "presumed optimal dosage regimen" was defined. The data on all bleeding episodes reported in the International Registry showed that the "optimal" regimen had a higher efficacy than other regimens. In the subgroup of patients with antibodies to GPIIb/IIIa and/or HLA and with platelet refractoriness, the number of evaluable bleeding episodes and surgical procedures is too small to compare the "presumed optimal regimen" with other dosage regimens. However, based on the demonstrated efficacy of the proposed regimen in the subgroup covered by the proposed therapeutic indication, the presently recommended dosage regimen seems acceptable. More insight in the efficacy of the proposed regimen could come from a post-marketing registry.

The benefit – risk relation for expanding the indication for NovoSeven was considered favourable. The condition for granting this marketing authorisation is the commitment of the MAH to establish a post-marketing registry of the treatment of patients with Glanzmann's thrombasthenia. In this registry the MAH should focus on the administered dosage regimens, efficacy and safety, especially the occurrence of thrombo-embolic complications in relation to the concomitant use of antifibrinolytics. Reporting from this post-marketing registry should be done every two years.

## **7. Extension of the indication in patients with FVII deficiency**

Congenital FVII deficiency is a rare autosomal recessive condition which was first described in 1951. Around 100 cases have been reported worldwide. Several different genetic variations of FVII deficiency have been described including those with and without cross-reacting material.

The bleeding pattern of FVII deficiency is very variable with some patients having a severe bleeding disorder mimicking haemophilia and including haemarthroses and others having mucocutaneous bleeding such as epistaxis, gastrointestinal bleeding and menorrhagia. Some patients with severe FVII deficiency do not appear to have a serious bleeding disorder. Patients with FVII deficiency have a prolonged prothrombin time and normal partial thromboplastin time.

Factor VII is coded on chromosome 13 and is a 406 amino acid vitamin K dependent glycoprotein produced in the liver. It is an initiator of the extrinsic pathway of coagulation and requires to complex with tissue factor to be activated, without the complex factor VII is not active.

Tissue factor is produced from endothelial cells at the site of injury and not much FVII is required to saturate it locally. In normal conditions about 1% of circulating FVII is activated to FVIIa. FVII has a short half-life of about 5.25 hrs. Large doses of FVIIa directly activate thrombin on the surface of the platelet and use a feedback mechanism to initiate the coagulation cascade.

Acquired FVII deficiency usually develops as a defect of vitamin K dependent clotting factors VII, IX and X in patients with liver disease or those on oral anticoagulation. Very rarely single factor VII deficiency can be acquired.

The current treatment of FVII deficiency is fresh frozen plasma, prothrombin complex concentrates and sometimes purified FVII where this is available.

The application was supported by pharmacodynamic and pharmacokinetic data in a limited number of FVII deficient patients. The clinical experience is predominantly based on three compassionate use programmes and one emergency use program with data on 32 patients with FVII deficiency (some patients suffered from acquired FVII deficiency) who were treated in 28 different sites in 6 countries between 1988 and 1999.

The limitations of such programmes are mainly inclusion of patients with acquired FVII deficiency, sparse details on the bleeding episodes, inconsistencies in the recording of data, variable dose regimens, limitations in the recording of concomitant medication, emphasis on the monitoring of efficacy and possible underreporting of (minor) adverse events.

At initiation of the compassionate/emergency use programmes, very limited experience was available on the treatment of patients with congenital FVII deficiency. Dosing was therefore individualised and based on the clinical assessment of the patient's status. Subsequently, patients with FVII deficiency were recommended to be treated with rFVIIa at a dose of 15-30 µg/kg every 4-6 hours until haemostasis was achieved. This recommendation was based on a pharmacodynamic study in two patients and a study of two patients who underwent surgery. Retrospective analysis of the extent of exposure to rFVIIa in the compassionate/emergency use programmes demonstrated that in the majority of patients the recommended dose regimen was followed: the median rFVIIa dose per injection was within the recommended dose range and the median number of injections per day administered was four consistent with the recommendation on posology. However, smaller and greater doses were used with effective outcome. It can be concluded that the data collected in the compassionate/emergency use program support the proposed dose range. However, the administration of rFVIIa must always be supervised by an experienced clinician and guided by individualised factors like the severity of the bleeding condition, the clinical efficacy and the level of FVII:C activity in the plasma of the patient.

There were two main concerns regarding the present application, the first one is the formation of inhibitory antibodies to FVIIa after the administration of rFVIIa in patients with congenital FVII deficiency. Three cases of antibody formation were reported with inhibitory antibodies in two of them. In one patient the antibody formation may have been caused by an accidental overdose of rFVIIa. The antibody formation was transient in a second patient. The CPMP is of the opinion that data on substitution therapy in FVII deficient patients are too scarce to draw any conclusions regarding the risk for antibody formation with a clinical consequence.

The second concern was the occurrence of thrombo-embolic complications, especially in patients predisposed to thrombotic events. These complications were not reported in the compassionate/emergency use program or in the literature but were reported during post-marketing experience in 3 patients. Therefore, the MAH will continue to closely monitor and review adverse events, especially thrombo-embolic complications and the development of antibodies, in patients with congenital FVII deficiency who are treated with rFVIIa.