PRODUCT MONOGRAPH

Schedule D

NiaStase RT®

eptacog alfa (activated)
Activated Recombinant Human Blood Coagulation Factor VII
Room Temperature Stable

Lyophilized Powder

1.0 mg per vial (50 KIU/vial)
2.0 mg per vial (100 KIU/vial)
5.0 mg per vial (250 KIU/vial)
8.0 mg per vial (400 KIU/vial)

Professed

Coagulation Factor

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Table of Contents

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous bolus injection	Lyophilized powder to be reconstituted for injection/ 1.0 mg (50 KIU) 2.0 mg (100 KIU) 5.0 mg (250 KIU) 8.0 mg (400 KIU)	calcium chloride dihydrate, glycylglycine, mannitol, methionine, polysorbate 80, sodium chloride, sucrose. The solvent for reconstitution of **NiaStase RT®** contains histidine in water for injections.
For a complete listing of nonmedicinal ingredients see DOSAGE FORMS, COMPOSITION AND PACKAGING section.		

DESCRIPTION

NiaStase RT® (eptacog alfa, activated) contains activated recombinant human blood coagulation Factor VII (**rFVIIa**) (eptacog alfa, activated). Recombinant Factor VII is a vitamin K-dependent glycoprotein consisting of 406 amino acids (MW approximately 50 K Dalton), which is structurally similar to human plasma-derived Factor VIIa.

INDICATIONS AND CLINICAL USE

NiaStase RT® (eptacog alfa, activated) is indicated:

- In hemophilia A/B patients with inhibitors to FVIII or FIX, respectively, for the treatment of bleeding episodes (including treatment and prevention of those occurring during and after surgery).

  Based on the data obtained so far with **rFVIIa** in the treatment of hemophilia patients with inhibitors, the apparent lack of anamnestic response during and after exposure to **rFVIIa** makes it suitable for use in all inhibitor patients.

- For the treatment of severe bleeding episodes in Glanzmann's thrombasthenia with clinical refractoriness and/or platelet-specific antibodies, or where platelets are not immediately available.

- For the prevention of bleeding in surgical interventions or invasive procedures in Glanzmann's thrombasthenia with clinical refractoriness and/ or platelet-specific antibodies, or where platelets are not readily available.

- In adult patients with acquired hemophilia, for the treatment of bleeding episodes, and for the prevention of bleeding in those undergoing surgery or invasive procedures.

- In patients with congenital Factor VII deficiency, for the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures.

CONTRAINDICATIONS

Known hypersensitivity to the active substance, the excipients, or to mouse, hamster or bovine protein may be a contraindication to the use of **NiaStase RT®** (eptacog alfa, activated).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Both arterial and venous thromboembolic adverse events have been reported after treatment with **rFVIIa**, mostly in patients with predisposing concurrent risk factors. (See *General* under WARNINGS AND PRECAUTIONS; Pharmacodynamics, under ACTION AND CLINICAL PHARMACOLOGY; ADVERSE REACTIONS).

- Reports of fatal and non-fatal outcomes, including those associated with thromboembolic events have been received during off-label use of **NiaStase RT®** (See *General* under WARNINGS and PRECAUTIONS).

- Patients with inherent Factor VII deficiency may have pre-existing or may develop anti-Factor VII antibodies during therapy with **NiaStase RT®**. The clinical significance of these antibodies is unknown. See ADVERSE REACTIONS section.

General

The extent of the risk of thrombotic adverse events after treatment with **rFVIIa** in patients with hemophilia and inhibitors is not known, but is considered to be low.

Patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with aPCCs/PCCs (activated or non-activated prothrombin complex concentrates) may have an increased risk of developing thrombotic events due to their underlying condition or concomitant treatment. Because of the risk of thromboembolic complications, caution should be exercised when administering **NiaStase RT®** (eptacog alfa, activated) to patients with a history of coronary heart disease, to patients with liver disease, to patients immobilised post-operatively, to neonates, or to patients at risk of thromboembolic phenomena or disseminated intravascular coagulation. In each of these situations, the potential benefit of treatment with **NiaStase RT®** should be weighed against the risk of these complications.

Safety and efficacy of **NiaStase RT®** have not been established outside the approved indications and therefore **NiaStase RT®** is not recommended. When **NiaStase RT®** is administered to patients outside the approved indications, arterial thromboembolic events are common (≥ 1/100 to < 1/10). A higher risk of arterial thromboembolic adverse events (5.3% in patients treated with **NiaStase RT®** versus 2.8% in placebo-treated patients) has been shown in a meta-analysis of pooled data from placebo controlled trials.

Clinical studies in non-hemophilia patients indicated an increased risk of arterial thromboembolic adverse events with the use of **rFVIIa** including myocardial infarction, myocardial ischemia, cerebral infarction and cerebral ischemia.

Factor VII deficient patients should be monitored for prothrombin time and Factor VII coagulant activity before and after administration of **NiaStase RT®**. In case the FVIIa activity fails to reach the expected level or bleeding is not controlled after treatment with the recommended doses, antibody formation may be suspected and analysis for antibodies should be performed. Thrombosis has been reported in FVII deficient patients receiving **NiaStase RT®** during surgery but the risk of thrombosis in FVII deficient patients treated with **NiaStase RT®** is unknown.

Patients who receive **NiaStase RT®** should be kept under close observation for signs and symptoms of unfavourable activation of the coagulation system or thrombosis. When there is laboratory confirmation of intravascular coagulation or presence of clinical thrombosis, the **NiaStase RT®** dosage should be reduced or treatment stopped, depending on the patient's symptoms.

Patients self-administering **NiaStase RT®** at home should be instructed not to exceed three doses. The duration of the ambulatory treatment should not exceed 24 hours. Patients should seek medical attention if bleeding is not controlled or if any unusual symptoms are experienced.

Patients receiving **NiaStase RT®** should be directed in its appropriate use and informed of the benefits and risks associated with treatment. If home use is prescribed, a puncture-resistant

container for the disposal of used syringes and needles should be supplied to the patient, and patients should be thoroughly instructed in the importance of proper disposal and cautioned against reuse of syringes and needles.

Hypersensitivity and anaphylaxis reactions have rarely been reported with the use of **rFVIIa**. Initial treatment with **NiaStase RT®** would always be under medical supervision, where emergency treatment for anaphylaxis can be rapidly applied. Patients should be monitored and warned about the early signs of hypersensitivity reactions and anaphylaxis, and asked to contact a physician if needed.

As **rFVIIa** may contain trace amounts of mouse IgG, bovine IgG and other residual culture proteins (hamster and bovine serum proteins), the remote possibility exists that patients treated with the product may develop hypersensitivity to these proteins. In such cases, treatment with i.v. antihistamines should be considered.

If allergic or anaphylactic-type reactions occur, the administration should be discontinued immediately. In case of anaphylactic shock, standard medical treatment for shock should be implemented. Patients should be informed of the early signs of hypersensitivity reactions. If such symptoms occur, the patient should be advised to discontinue use of the product immediately and contact their physician.

Carcinogenesis and Mutagenesis

No chronic carcinogenicity studies have been performed with **NiaStase RT®**. Two mutagenicity studies have given no indication of carcinogenic potential for **rFVIIa**. See TOXICOLOGY.

Special Populations

Pregnant Women:
As a precautionary measure it is preferable to avoid the use of **NiaStase RT®** during pregnancy. Data on a limited number of exposed pregnancies indicate no adverse effects of **rFVIIa** on pregnancy or on the health of the fetus/new-born child. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development (see TOXICOLOGY).

In patients receiving **rFVIIa** during delivery or post-partum, thrombotic events such as myocardial infarction, pulmonary embolism, deep venous thrombosis, retinal artery occlusion, or cerebral ischemia were observed. In this period, patients are at increased risk for thrombotic complications. It is not known to which extent **rFVIIa** contributes to the occurrence of these events. No specific preventive actions can be recommended.

Nursing Women:
It is unknown whether **rFVIIa** is excreted in human breast milk. The excretion of **rFVIIa** in milk has not been studied in animals. A decision on whether to continue/discontinue breast-

feeding or to continue/discontinue therapy with **NiaStase RT**® should be made taking into account the benefit of breast-feeding to the child and the benefit of **NiaStase RT**® therapy to the woman.

Pediatric Patients (birth to 16 years of age):
Evidence for the safety and effectiveness of **rFVIIa** has been obtained in the age groups up to adolescence (up to 16 years of age). When dosed on a body weight basis, the efficacy and safety of **rFVIIa** appear to be comparable in adult and pediatric patients. Available clinical trials and post marketing data show a faster clearance of FVII in children. However, the data are insufficient to support the recommendation of higher doses in children (see ACTION AND CLINICAL PHARMACOLOGY/Pharmacokinetics).

The safety and efficacy of **NiaStase RT**® in patients <17 years with acquired hemophilia have not been established.

Geriatric Patients (≥65 years of age):
Clinical studies of **NiaStase RT**® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Monitoring and Laboratory Tests

It should be noted that the therapeutic range of **rFVIIa** for hemostasis has not been identified in tests for prothrombin time (PT), aPTT, and plasma FVII clotting activity (FVII:C). For these reasons, coagulation parameters should be used only as an adjunct to the evaluation of clinical hemostasis to monitor the effectiveness and treatment schedule of **NiaStase RT**® in patients.

Monitoring the effectiveness of therapy, the need for additional doses of **NiaStase RT**® or a change to alternative therapy should be based on the changes in the clinical parameters of pain, swelling and joint mobility compared to baseline or, if following improvement in any of the above parameters; symptoms of a rebleed are present.

Criteria for Administration of Additional Treatment	
Subjects with persistent moderate or severe pain following **rFVIIa** treatment	Subjects with persistent mild pain following **rFVIIa** treatment
One or more of the clinical assessments (1 to 4) is fulfilled	Two or more of the clinical assessments (1 to 4) are fulfilled
1. Pain judged same/worse. 2. Swelling (evident before treatment as compared to baseline) judged same/worse. 3. Joint mobility (evident before treatment as compared to baseline) judged same/worse. 4. Following improvement in either pain, swelling or joint mobility; signs or symptoms of a rebleed are present.	

There is no requirement for monitoring of **NiaStase RT®** therapy. Severity of bleeding condition and clinical response to **NiaStase RT®** administration must guide dosing requirements.

After administration of **rFVIIa**, prothrombin time (PT) and activated partial thromboplastin time (aPTT) have been shown to shorten, however, no correlation has been demonstrated between PT and aPTT and clinical efficacy of **rFVIIa**.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most serious adverse drug reactions observed in patients receiving **rFVIIa** are thrombotic events, however the extent of the risk of thrombotic adverse events after treatment with **rFVIIa** in individuals with congenital hemophilia with inhibitors is considered to be low.

The most common adverse drug reactions observed in patients with congenital hemophilia A or B with inhibitors are pyrexia, injection site reaction, headache, hypertension, hypotension, nausea, vomiting, pain, edema and rash. See WARNINGS AND PRECAUTIONS.

In a compassionate use program an increased risk of thromboembolic adverse reactions in patients with acquired hemophilia was observed, compared to patients with congenital hemophilia with inhibitors.

Patients who receive **NiaStase RT®** (eptacog alfa, activated) should be kept under close observation for signs and symptoms of unfavourable activation of the coagulation system or thrombosis.

Clinical Trial Adverse Drug Reactions in Congenital Hemophilia A/B Patients with Inhibitors

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

During clinical studies in 298 hemophilia A/B patients with inhibitors involving 1,939 bleeding episodes, there were 182 adverse reactions that were possibly related or of unknown relationship to **rFVIIa**. Of these, there were 21 serious adverse reactions that were possibly related or of unknown relation to treatment reported in 14 patients, and included 6 deaths. During the clinical program, 4 episodes of clinical or laboratory evidence of DIC were documented in hemophilia patients with inhibitors.

In the clinical studies, thrombogenicity has been associated rarely with the use of **rFVIIa** (11 events out of 1,939 treatment episodes for an incidence of <1%). Thrombosis was reported in two of the 298 patients with hemophilia.

In 175 surgical procedures with **rFVIIa**, three thrombotic events occurred - one thrombosis, one episode of phlebitis and one patient with a large abscess and sepsis died of DIC. In the clinical testing program, isolated cases of antibody development have been reported in FVII deficient patients after treatment with **rFVIIa**.

No severe allergic reactions have occurred in hemophilia patients receiving **rFVIIa**. Additionally, the potential for development of antibodies towards **rFVIIa** has been followed in hemophilia A/B patients and in none of these cases have antibodies towards **rFVIIa** or other potentially antigenic components of the drug product (BHK-cell protein, murine IgG, or bovine serum) been detected.

In a clinical study comparing the safety and efficacy of **rFVIIa** when administered through bolus injection versus continuous infusion to hemophiliacs with inhibitors during and after surgery, seven of 24 patients had serious adverse events (4 for bolus injection, 3 for continuous infusion). There were 4 serious adverse events which were considered probably or possibly related to **rFVIIa** treatment (2 events of decreased therapeutic response in each treatment arm). No deaths occurred during the study period.

Table 1 – Adverse events that were reported in ≥ 1% of rFVIIa Treatment Episodes and were considered to be possibly related to rFVIIa administration.

Body System	Number of Adverse Events reported n= 1,939 treatments (%)
Body as a whole	(2)
Fever	16 (1)
Platelets, Bleeding, and Clotting	(3)
Hemorrhage NOS	15 (1)
Fibrinogen plasma decreased	10 (1)
Skin and Musculoskeletal	(2)
Hemarthrosis	14 (1)
Nervous System	15 (1)
Cardiovascular	18 (1)

Less Common Clinical Trial Adverse Drug Reactions (< 1%) in Congenital Hemophilia A/B Patients with Inhibitors

Gastrointestinal: < 1 %
Liver and biliary: < 1 %
Metabolic and Endocrine: < 1 %
Respiratory: < 1 %
Urinary: < 1 %
Application Site: < 1 %
Resistance mechanism: < 1 %
Other: < 1 %

Abnormal Hematologic and Clinical Chemistry Findings in Congenital Hemophilia A/B Patients with Inhibitors

Table 2 – Coagulation Parameter Shifts

Parameter	Shift*	No. of Treatment Episodes Experiencing Shift (%)	Total No. of Treatment Episodes Evaluated
D-Dimer	Normal to High	17 (15)	112
Fibrinogen	Normal to Low High to Low	27 (9)	288
Platelets	Normal to Low High to Low	28 (8)	365

* Refers to potential clinically significant shift during the study. A shift to D-dimer values higher than the normal range may be clinically significant, while a shift to fibrinogen and platelet values lower than normal range may be clinically significant.

Table 3 – Clinical Chemistry Parameter Shifts

Parameter	Shift*	No. of Treatment Episodes Experiencing Shift (%)	Total No. of Treatment Episodes Evaluated
Alkaline Phosphatase	Normal to High	14 (12)	112
ALT	Normal to High	12 (12)	102
AST	Normal to High	11 (10)	108
LDH	Normal to High	8 (9)	85
Creatinine	Normal to High	4 (3)	137

* Refers to potential clinically significant shift during the study. Increases to values above the normal range in alkaline phosphatase, ALT, AST and LDH may indicate changes in liver function, while increase in creatinine may indicate renal function changes.

Adverse Drug Reactions in Patients with Acquired Hemophilia

Data collected in 61 acquired hemophilia patients with a total of 100 bleeding episodes, participating in a compassionate use program for acquired hemophilia, showed that certain adverse drug reactions were reported more frequently (1% based on treatment episodes): Arterial thromboembolic events (cerebral artery occlusion, cerebrovascular accident), venous thromboembolic events (pulmonary embolism and deep vein thrombosis), angina pectoris, nausea, pyrexia, erythematous rash and investigation of increased levels of fibrin degradation products. For 2 out of 4 patients who suffered a serious adverse drug reaction the outcome was fatal (cerebral artery occlusion and circulatory shock).

In the clinical studies, thrombogenicity was associated with the use of **rFVIIa** more frequently in the acquired hemophilia population (4 events out of 100 treatment episodes for an incidence of 4%), compared to 0.6% (11 events out of 1,939 treatment episodes) in patients with congenital hemophilia with inhibitors. Thrombosis was reported in two of the 61 patients with acquired hemophilia.

Adverse Drug Reaction Overview in Clinical Trials using NiaStase RT®

The safety profile of **NiaStase RT®** administered to achieve or maintain hemostasis has not been assessed in clinical trials. However, the short term safety profile and the tolerability of a single dose of **NiaStase RT®** were investigated in the NN1007-1744 and NN1007-1862 trials, which included non-bleeding healthy subjects and patients with hemophilia, respectively. A total of 25 subjects were exposed to a single dose of **NiaStase RT®** (24 subjects) and/or **NiaStase®** (24 subjects) in the NN1007-1744 trial. A total of 24 patients with hemophilia were exposed to a single dose of **NiaStase RT®** in the NN1007-1862 trial.

Overall, the results of the clinical trials do not suggest any alteration to the established **rFVIIa** safety profile, or any additional risk of thromboembolic complications or antibody formation. There were no clinically relevant findings in other safety parameters including local tolerability, physical examination, vital signs and laboratory parameters. In addition, the documented equivalence of the pharmacokinetic profiles substantiates equivalent or similar safety of **NiaStase RT®** and **NiaStase®** (see CLINICAL TRIALS, Comparative Bioavailability Studies).

Post-Market Adverse Drug Reactions

Post-marketing adverse drug reactions are reported voluntarily from a population of uncertain size; hence, it is not possible to estimate their frequency or establish a causal relationship to exposure. Adverse drug reactions reported post-marketing only (i.e. not in clinical trials) are presented in the table below with a frequency of "not known".

When analyzed by system organ classes, the reporting rates of adverse drug reactions, including both serious and non-serious reactions, are as indicated in the table below.

Table 4 - Reporting Rates of Post-marketing Adverse Drug Reactions

Post-Market Adverse Drug Reactions	
Blood and lymphatic disorders	
Rare (≥1/10,000, < 1/1,000)	- Disseminated intravascular coagulation and related laboratory findings including elevated levels of D-dimer and decreased levels of AT - Coagulopathy
Gastrointestinal disorders	
Rare (≥1/10,000, <1/1,000)	- Nausea
General disorders and administration site conditions	
Uncommon (≥1/1,000, <1/100) Rare (≥1/10,000, < 1/1,000)	- Therapeutic response decreased* - Pyrexia - Injection site reaction including injection site pain *Lack of efficacy (therapeutic response decreased) has been reported. It is important that the dosage regimen of **NiaStase RT**® is compliant with the recommended dosage as stated. See DOSAGE AND ADMINISTRATION.
Immune system disorders	
Rare (≥1/10,000, < 1/1,000) Not known	- Hypersensitivity - Anaphylactic reaction
Investigations	
Rare (≥1/10,000, < 1/1,000)	- Increased fibrin degradation products - Increase of alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase and prothrombin.
Nervous system disorders	
Rare (≥1/10,000, < 1/1,000)	- Headache
Skin and subcutaneous tissue disorders	
Uncommon (≥ 1/1,000, < 1/100) Not known	- Rash (including allergic dermatitis and rash erythematous) - Pruritus and urticaria - Flushing - Angioedema
Vascular disorders	
Rare (≥ 1/10,000, < 1/1,000) Uncommon (≥ 1/1,000, < 1/100)	- Arterial thromboembolic events: (myocardial infarction, cerebral infarction, cerebral ischemia, cerebral artery occlusion, cerebrovascular accident, renal artery thrombosis, peripheral ischemia, peripheral arterial thrombosis and intestinal ischemia) - Angina pectoris - Venous thromboembolic events: (deep vein thrombosis, thrombosis at i.v. site, pulmonary embolism, thromboembolic events of the liver

Post-Market Adverse Drug Reactions	
	including portal vein thrombosis, renal vein thrombosis, thrombophlebitis, superficial thrombophlebitis and intestinal ischemia)
Not known	- Intracardiac thrombus Thromboembolic events may lead to cardiac arrest.

Inhibitory Antibody Formation

In post-marketing and clinical experience, there have been no confirmed reports of inhibitory antibodies against **NiaStase RT®** or FVII in hemophilia A or hemophilia B patients. Development of inhibitory antibodies to **NiaStase RT®** has been reported in a post-marketing observational registry of patients with congenital Factor VII deficiency (see Post-Market Adverse Drug Reactions, Congenital Factor VII Deficiency).

In clinical trials of patients with Factor VII deficiency, formation of antibodies against **NiaStase RT®** and FVII is the only adverse drug reaction reported (frequency: common (≥ 1/100 to < 1/10)). In some cases, the antibodies showed inhibitory effect *in vitro*. Risk factors that may have contributed to antibody development including previous treatment with human plasma and/or plasma-derived Factor VII, severe mutation of FVII gene, and overdose of **NiaStase RT®** were present. Patients with Factor VII deficiency treated with **NiaStase RT®** should be monitored for FVII antibodies (see WARNINGS AND PRECAUTIONS, General).

Glanzmann's Thrombasthenia

Data collected from the Glanzmann's Thrombasthenia Registry (GTR) and the Hemostasis and Thrombosis Research Society (HTRS) registry showed that 140 patients with Glanzmann's thrombasthenia received **NiaStase RT®** for 518 bleeding episodes, surgeries or traumatic injuries.

In the GTR one patient reported a serious adverse reaction (deep vein thrombosis) and one patient experienced three adverse reactions (nausea, headache and dyspnea). In addition, two patients experienced fever and one patient experienced headache where the temporal relationship suggests a possible causal relationship to **NiaStase RT®**. No adverse reactions were reported for Glanzmann's thrombasthenia patients in the HTRS registry.

An additional 19 adverse reactions in 12 patients have been identified in the literature and from spontaneous reports to Novo Nordisk. These include drug ineffective in five patients (one patient received **NiaStase RT®** via continuous infusion), seven thromboembolic events in three patients (one patient received **NiaStase RT®** via continuous infusion), angioedema in two patients and ureteric obstruction in one patient receiving a continuous infusion. Additionally, one patient experienced nausea and vomiting, one patient urticaria, and another patient experienced increased hepatic enzyme levels.

Acquired Hemophilia

Data from 378 patients with acquired hemophilia who were treated with **rFVIIa** was collected from the European Acquired Hemophilia (EACH2) Registry, the Hemostasis and Thrombosis Research Society (HTRS) Registry, and a Japanese Post-Marketing Surveillance Study (JPMS). Adverse events were collected according to protocol in each registry. An increased risk of thromboembolic adverse reactions compared to congenital hemophilia patients was observed (10 events out of 710 treatment episodes for an incidence of <2%). Thrombosis was reported in 9 of the 378 patients.

Congenital Factor VII Deficiency

Data from 194 patients with congenital Factor VII deficiency who were treated with **rFVIIa** was collected from the Seven Treatment Evaluation Registry (STER) and the Novo Nordisk compassionate/emergency use program. Adverse events were collected according to the individual protocols.

In the STER registry, a total of 16 adverse events were reported in 12 patients. A total of 3 thrombotic adverse events were seen in 3 patients. Of these, 2 were reported as 'Cerebrovascular Reactivity / Transient Ischemic Attack' (one of them was serious) and both were considered probably related to **rFVIIa** by the investigator. The other non-serious event concerned a thrombosis in the injection site. All 3 patients had an underlying condition (trauma or intracerebral hematoma) which might have contributed to the events. There was no evidence of a generalized activation of the coagulation system. The 3 thrombotic events were observed across a total of 240 admissions (incidence: 1.25%).

Adverse events of inhibitory antibodies against FVII were recorded in 2 patients. Both patients had a good clinical response to treatment with **rFVIIa** during the following study period. There were no anaphylactic reactions. Overall, no new safety concerns were identified in patients with congenital Factor VII deficiency treated with **rFVIIa** in the STER registry.

In the compassionate/emergency use program, a total of 15 serious adverse events were reported in 9 out of 32 patients. All serious adverse events were considered to be unlikely related to treatment with **rFVIIa**, except 1 event of antibody development against FVII. One event of antibodies against FVII was also reported spontaneously after finalization of the trial. No thrombotic complications were reported in the 69 treatment episodes. Overall, administration of **rFVIIa** in the compassionate/emergency use program did not give rise to any safety concerns in the patients treated.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Healthcare providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Health Product Safety Information Division at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit.

DRUG INTERACTIONS

Serious Drug Interactions

- **NiaStase RT®** (eptacog alfa, activated) should not be mixed with infusion solutions or be given in a drip.
- Simultaneous use of prothrombin complex concentrates, activated or not, should be avoided.

Overview

The risk of a potential interaction between **NiaStase RT®** and coagulation factor concentrates is unknown.

Anti-fibrinolytics have been reported to reduce blood loss in association with surgery in hemophilia patients, especially in orthopedic surgery and surgery in regions rich in fibrinolytic activity, such as the oral cavity. Experience with concomitant administration of anti-fibrinolytics and **rFVIIa** treatment is, however, limited.

Drug-Drug Interactions

A potential synergistic effect of combined treatment with rFXIII (17 times the recommended human dose) and **rFVIIa** (11 times the recommended human dose) in an advanced cardiovascular model in cynomolgus monkey was seen resulting in exaggerated pharmacology (thrombosis and death) at a lower dose level than when administering the individual compounds.

Based on the non-clinical study it is not recommended to combine **rFVIIa** and rFXIII. There are no clinical data available on the interaction between **rFVIIa** and rFXIII.

Interactions with other drugs have not been established.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Changes in D-Dimer, Fibrinogen, Platelets, Alkaline Phosphatase, ALT, AST, LDH and Creatinine were seen in clinical trials. See ADVERSE REACTIONS – Abnormal Hematologic and Clinical Chemistry Findings.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia and/or bleeding disorders.
- In case of severe bleeds the product should be administered in hospitals preferably specialized in treatment of hemophilia patients with coagulation factor VIII or IX inhibitors, or if not possible in close collaboration with a physician specialized in hemophilia treatment.
- Hemostasis evaluation should be used to determine the effectiveness of **NiaStase RT®** (eptacog alfa, activated) and to provide a basis for modification of the **NiaStase RT®** treatment schedule.
- **NiaStase RT®** should be given as early as possible after the start of a bleeding episode. Following the initial dose of **NiaStase RT®** further injections may be repeated. The duration of treatment and the interval between injections will vary with the severity of the hemorrhage, the invasive procedures or surgery being performed.
- In hereditary severe FVII-deficient patients, replacement therapy with **NiaStase RT®** in doses of 15 to 30 µg/kg at 4 to 6 hour intervals has been shown to significantly shorten or normalize prothrombin time. However, no correlation has been demonstrated between PT and aPTT and clinical efficacy of **NiaStase RT®**.

Recommended Dose and Dosage Adjustment

NiaStase RT® is intended for intravenous bolus administration only. The recommended dose range, dose, frequency, and duration of **NiaStase RT®** administration as a single agent are outlined below. Coagulation parameters should not be used to evaluate **NiaStase RT®** effectiveness.

Congenital Hemophilia A or B with Inhibitors

Indication	Recommended Dose	Frequency and Duration
Bleeding episodes	90 µg/kg*	• An initial dose of 90 µg/kg is recommended. • Dose may vary depending on bleed severity (see dose range). • Administer every 2 hours until clinical improvement is observed. • If continued therapy is required, the dosage interval may be increased from 2 to 6 hours depending on the period of time the treatment is judged to be indicated.
Surgery	90 µg/kg	• An initial dose of 90 µg/kg is recommended. • Dose may vary depending on surgery type (see dose range). • Administer prior to surgery and at least every 2 hours during the procedure. • Dosing should be repeated every 2 hours for the first 24-48 hours after surgery, depending on the surgery performed and the clinical status of the patient. • Dosing may be repeated once during the 2-hour interval after surgery depending on the clinical status of the patient. • If continued therapy is required, the dosage interval may be increased from 2 to 6 hours depending on the period of time the treatment is judged to be indicated.

* Doses between 35 and 120 µg/kg have been used successfully in clinical trials for hemophilia A or B patients with inhibitors, and both the dose and administration interval may be adjusted based on the severity of the bleeding and degree of hemostasis achieved.

Glanzmann's Thrombasthenia

Indication	Recommended Dose	Frequency and Duration
Treatment of severe bleeding episodes	90 µg/kg	• A dose of 90 µg/kg repeated every 2-6 hours until hemostasis is achieved. • **NiaStase RT®** can be used alone or in combination with other hemostatic agents (e.g. antifibrinolytics) and/or transfusion of matched platelets.
Prevention of bleeding during surgery	90 µg/kg*	• An initial dose of 90 µg/kg given immediately before the intervention and repeated at 2-hour intervals for the duration of the surgery. • Post-surgical doses should be administered at 2-6 hour intervals to prevent post-operative bleeding.

* Higher average infused doses (median dose was 100 µg/kg (IQR 90-140)) were noted for surgical patients who had clinical refractoriness with or without platelet-specific antibodies compared to those with neither.

The minimum effective dose for the treatment of bleeding episodes and prevention of bleeding during surgery in Glanzmann's thrombasthenia has not been determined.

In patients without refractoriness to platelets or in patients without platelet-specific antibodies platelets are the primary treatment. In these patients, **NiaStase RT®** should be reserved for treatment when platelets are not immediately or readily available.

Acquired Hemophilia

Indication	Recommended Dose	Frequency and Duration
Bleeding episodes and surgery	90 µg/kg	• The recommended initial dose, administered by intravenous bolus injection, is 90 µg per kg body weight. • The initial dose interval should be 2-3 hours. • Once hemostasis has been achieved, the dose interval can be increased successively to every 4, 6, 8 or 12 hours for as long as treatment is judged to be indicated.

Congenital Factor VII Deficiency

Indication	Recommended Dose	Frequency and Duration
Bleeding episodes	15-30 µg/kg	• The recommended dose range for treatment of bleeding episodes is 15-30 µg/kg every 4-6 hours until hemostasis is achieved. • Dose and frequency of injections should be adapted to each individual.
Surgery	15-30 µg/kg	• The recommended dose range for the prevention of bleeding in patients undergoing surgery or invasive procedures is 15-30 µg/kg immediately before surgery, and repeat every 4-6 hours for the duration of the surgery and until hemostasis is achieved. • Dose and frequency of injections should be adapted to each individual.

Reconstitution

Calculate the **NiaStase RT®** dosage you will need and select the appropriate **NiaStase RT®** package. The selected package contains 1 vial of **NiaStase RT®** powder, accompanied by a prefilled syringe containing histidine solvent, which is required to prepare and reconstitute the **NiaStase RT®** powder. Reconstitute only with the histidine solvent provided with **NiaStase RT®**. **Do not reconstitute with sterile water or other solvents.**

The specified volume of histidine solvent corresponding to the amount of **NiaStase RT®** is given below.

NiaStase RT® package containing 1 vial of **NiaStase RT®** powder and 1 prefilled syringe of histidine solvent

NiaStase RT® Vial Size (mg)	Volume of Histidine Solvent to be Added to NiaStase RT® Vial (mL)	Approximate Concentration of rFVIIa After Reconstitution (mg per mL)
1	1	1
2	2	1
5	5	1
8	8	1

For detailed instructions on how to reconstitute **NiaStase RT®** refer to PART III of the Product Monograph.

Administration

For storage conditions of the reconstituted product refer to STORAGE AND STABILITY/After reconstitution.

If **NiaStase RT**® is being reconstituted in a hospital setting (i.e. under controlled and validated aseptic conditions) and stored in a polypropylene syringe, it is recommended to use an in-line filter with a pore size of 25 micrometer upon administration.

NiaStase RT® is intended for intravenous bolus injection only and should not be mixed with infusion solutions or be given in a drip. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever the solution and container permit. Do not use if particulate matter or discolouration is observed.

Injecting **NiaStase RT**® with prefilled syringe (MixPro®) via needleless connectors for intravenous (IV) catheters

The prefilled solvent syringe with sterile vial adapter, together serve as a needleless reconstitution system named the MixPro®.

Caution: The MixPro® prefilled solvent syringe is made of glass and is designed to be compatible with standard luer-lock connections. Some needleless connectors with an internal spike are incompatible with the prefilled syringe. This incompatibility may prevent administration of the drug and/or result in damage to the needleless connector.

Follow the instructions for use that come with the needleless connector. Administration through a needleless connector may require withdrawal of the reconstituted solution into a standard 10 mL sterile luer-lock plastic syringe.

If you have encountered any problems with attaching the prefilled histidine solvent syringe to any luer-lock compatible device, or have any questions please contact Novo Nordisk at 1-800-465-4334.

For detailed instructions on how to administer **NiaStase RT**® refer to PART III of the Product Monograph.

OVERDOSAGE

Dose limiting toxicities of **rFVIIa** have not been investigated in clinical trials.

The following are examples of accidental overdose. One hemophilia B patient (16 years of age, 68 kg) received a single dose of 352 µg/kg, and one hemophilia A patient (2 years of age, 14.6 kg) received doses ranging from 246 µg/kg to 986 µg/kg on five consecutive days. There were no reported complications in either case. One newborn female congenital FVII-deficient patient (7 weeks of age, 3 kg) received one dose of 800 µg/kg and 8 doses of 400 µg/kg and subsequently developed antibodies to FVII. No thrombotic complications as a result of the overdosages were reported.

A Factor VII deficient male (83 years of age, 111.1 kg) received two doses of 324 µg/kg (10-20 times the recommended dose) and experienced a thrombotic event (occipital stroke). In addition, the development of antibodies against **rFVIIa** and FVII, has been associated with overdose in patients with Factor VII deficiency.

No cases of overdose have been reported in patients with Glanzmann's thrombasthenia or with acquired hemophilia.

In addition, 16 normal volunteers in a dose escalation study received doses up to 320 µg/kg without serious adverse reactions.

The recommended dose schedule should not be intentionally increased, even in the case of lack of effect, due to the absence of information on the additional risk that may be incurred.

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

NiaStase RT® (eptacog alfa, activated), when complexed with tissue factor at the site of injury, activates coagulation Factor X (to Factor Xa), as well as coagulation Factor IX (to Factor IXa). Factor Xa then converts prothrombin to thrombin. Thrombin leads to the activation of platelets and Factors V and VIII at the site of injury and to the formation of the hemostatic plug by converting fibrinogen into fibrin. Pharmacological doses of **NiaStase RT®** activate Factor X directly on the surface of activated platelets, localized to the site of injury, independently of tissue factor. This results in the conversion of prothrombin into large amounts of thrombin independently of tissue factor. Accordingly, the pharmacodynamic effect of Factor VIIa gives rise to an increased local formation of Factor Xa, thrombin and fibrin. Because **NiaStase RT®** can activate Factor X independent of Factor VIII and IX activity, it can be used for the management of bleeding episodes and surgery in patients with inhibitors to coagulation Factors VIII or IX.

A theoretical risk for the development of systemic activation of the coagulation system in patients suffering from underlying diseases predisposing them to DIC cannot be totally excluded.

Pharmacokinetics

Healthy Subjects
Using the FVII clotting assay, the pharmacokinetics of **rFVIIa** were investigated in 35 healthy Caucasian and Japanese subjects in a dose-escalation study. Subjects were stratified according to gender and ethnic group and dosed with 40, 80 and 160 µg **rFVIIa** per kg body weight and/or placebo (3 doses each). The pharmacokinetic profiles indicated dose proportionality. The pharmacokinetics were similar across gender and ethnic groups. The mean steady state volume of distribution ranged from 130 to 165 mL/kg, the mean values of clearance ranged from 33.3 to 37.2 mL/h x kg, and the mean terminal half-life ranged from 3.9 to 6.0 hours.

Congenital Hemophilia A and B with Inhibitors
Using the FVIIa assay, the pharmacokinetic properties of **rFVIIa** were studied in 12 pediatric (2-12 years) and 5 adult patients in non bleeding state. Dose proportionality was established for the investigated doses of 90 and 180 µg per kg body weight, which is in accordance with previous findings at lower doses (17.5 - 70 µg/kg **rFVIIa**). Mean clearance was approximately 50% higher in pediatric patients relative to adults (78 versus 53 mL/h x kg), whereas the mean terminal half life was determined to 2.3 hours in both groups. Mean volume of distribution at steady state was 196 mL/kg in pediatric patients versus 159 mL/kg in adults.

Glanzmann's thrombasthenia
The pharmacokinetics of **rFVIIa** in patients with Glanzmann's thrombasthenia has not been investigated.

Congenital Factor VII Deficiency
Single dose pharmacokinetics of **rFVIIa**, 15 and 30 µg per kg body weight (in 5 subjects), showed a volume of distribution at steady state (280 – 290 mL/kg), half-life (2.82 - 3.11 h), total body clearance (70.8 - 79.1 mL/h×kg) and mean residence time (3.75 - 3.80 h). The mean *in vivo* plasma recovery was approximately 20%.

STORAGE AND STABILITY

Prior to reconstitution
Keep **NiaStase RT®** powder and the histidine solvent refrigerated or store between 2° to 25°C. Do not freeze. Protect powder and solvent from light. Do not use past the expiration date.

After reconstitution
Do not freeze reconstituted **NiaStase RT®**.

In vial: After reconstitution, chemical and physical stability has been demonstrated for 6 hours at 25°C and 24 hours at 5°C. From a microbiological point of view, the product should be used immediately unless reconstitution has taken place in controlled and validated aseptic conditions.

If not used immediately, storage time and storage conditions prior to use are the responsibility of the user, and should not be longer than 24 hours at 2°C – 8°C. The reconstituted solution should be stored in the vial.

Use of polypropylene syringe in hospital settings: After reconstitution, chemical and physical stability has been demonstrated for 24 hours at 25°C when stored in a polypropylene syringe. The product should only be stored in a polypropylene syringe if reconstitution has taken place in controlled and validated aseptic conditions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

NiaStase RT® (eptacog alfa, activated) is supplied as a white, lyophilized powder in single-use vials. The solvent for reconstitution of **NiaStase RT®** is a 10 mmol solution of histidine in water for injection and is supplied in a prefilled syringe, as a clear colourless solution. Not all presentations and pack sizes may be marketed.

The **NiaStase RT®** package contains:

- 1 vial with white powder for solution for injection
- 1 prefilled syringe with solvent for reconstitution
- 1 plunger rod
- 1 vial adapter for reconstitution

The prefilled solvent syringe with sterile vial adapter, together serve as a needleless reconstitution system named the MixPro®.

The amount of **rFVIIa** in milligrams and kilo-international units is stated on the label as follows:

- 1.0 mg per vial (50 KIU/vial)
- 2.0 mg per vial (100 KIU/vial)
- 5.0 mg per vial (250 KIU/vial)
- 8.0 mg per vial (400 KIU/vial)

The following non-medicinal ingredients are found in **NiaStase RT®**: calcium chloride dihydrate, glycylglycine, mannitol, methionine, polysorbate 80, sodium chloride, and sucrose.

After reconstitution 1 mL of solution contains 10 mg of sucrose.

Vials: Made of Type 1 glass, closed with a latex-free, chlorobutyl rubber stopper, and covered with an aluminum cap. The vials are equipped with a tamper-evident snap-off polypropylene cap.

Prefilled syringe: Made of Type I glass barrel with a polypropylene backstop and bromobutyl rubber plunger. The syringe cap consists of bromobutyl rubber and polypropylene tamper evident seal.

Plunger rod: Made of polypropylene.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	eptacog alfa (activated)
Chemical name:	activated recombinant coagulation Factor VII
Molecular formula and molecular mass:	$C_{1982}H_{3054}N_{560}O_{618}S_{28}$, approximately 50 KD
Structural formula:	A polypeptide consisting of 406 amino acids. **rFVIIa** is the two chain form of rFVII generated by a cleavage of the peptide bond between amino acids in position 152 and 153. The two chains are held together by a single disulphide bridge. The molecule is glycosylated at the amino acids in position 52, 60, 145 and 322, and γ-carboxylated in the Glu-residues (partial γ-carboxylation in position 35).
Physicochemical properties:	
Description:	The powder for injection is a white lyophile, and the reconstituted preparation is a colourless solution.
Isoelectric Point:	At pH 6.0-6.7
	1 KIU equals 1000 International Units (IU).

Product Characteristics

Human FVII was cloned and expressed in baby hamster kidney (BHK) cells.

Recombinant Factor VII is secreted from BHK cells and converted to the active form (Recombinant Factor VIIa) during the purification process. **NiaStase RT**® (eptacog alfa, activated) is structurally similar to human plasma-derived Factor VIIa.

Production of **NiaStase RT**® via recombinant DNA technology eliminates the risks of transmission of human blood-borne pathogens such as HIV, hepatitis viruses and parvovirus.

CLINICAL TRIALS

Congenital Hemophilia A or B with Inhibitors

No clinical studies were conducted with **NiaStase RT®** in patients with congenital hemophilia and inhibitors. All clinical studies in patients with congenital hemophilia and inhibitors were previously conducted with **NiaStase®**. To support use of **NiaStase RT®** in this patient population, a single dose bioequivalence pharmacokinetic study (NN1007-1744) in healthy male subjects was conducted to compare **NiaStase RT®** to **NiaStase®** (see Comparative Bioavailability Studies).

Five adequate and well-controlled studies (see Table 5) and several supporting studies have provided substantial evidence for the efficacy of **rFVIIa**. In these trials hemophilia patients with inhibitors were treated with **rFVIIa** for several types of bleeding episodes and for hemostasis during surgical procedures. The efficacy rates of **rFVIIa** are shown in Table 7.

These efficacy results are consistent with results obtained in supporting clinical studies (see Table 6) with **rFVIIa**.

Study Demographics and Trial Design

Table 5 – Congenital Hemophilia A/B Patients with Inhibitors in Adequate and Well-Controlled Clinical Studies

Study #	Trial design	Dosage, route of administration and duration	No. of Patients	No. of Bleeding Episodes	Efficacy Endpoint
F7HAEM/USA/3/USA Surgical	Double-blind Randomized Multicenter	35 or 90 µg/kg presurgery. Every 2 hrs for 48 hrs, then every 2 to 6 hrs	28	28 surgeries - 17 minor - 11 major	Investigator evaluation of hemostasis
F7HT/USA/1/US At Home Treatment	Open Label Multicenter	90 µg/kg Every 3 hrs for up to 4 doses	56	877	Investigator/patient/ staff evaluation of hemostasis
F7HAEM/USA/2/USA Life and Limb-Threatening Bleeds	Open Label Multicenter Patients unresponsive to alternative therapies	90 µg/kg Every 2 hrs until clinical improvement, or preorthopedic and postorthopedic rehabilitative therapy	127	253	Investigator evaluation of hemostasis
USA/VII/006/DOS-REV Dose Finding	Double-blind Randomized Multicenter	35 or 70 µg/kg Every 2.5 hrs up to 6 doses	66	153 (Primary bleeds)	Investigator evaluation of hemostasis
HAEM-2011 Surgical	Open-Label, Randomized, Parallel, multi-centre	**Prior to surgery** 90 µg/kg bolus dose for both groups, followed by: **The bolus injection group** During procedure and Days 1-5: 90 µg/kg every 2 hours; Days 6-10: 90 µg/kg every 4 hours **The continuous infusion group** Days 1-5: 50 µg/kg/h; Days 6 - 10: 25 µg/kg/h	36	36 (major surgeries)	Investigator evaluation of hemostasis.

Table 6 – Congenital Hemophilia A/B Patients with Inhibitors in Supporting Studies of Efficacy

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	No. of Bleeding Episodes	Efficacy Endpoint
USA/VII/006/DOS	Double-Blind Multicenter	35 or 70 µg/kg every 3 to 4 hrs	11	25	Investigator evaluation of hemostasis
001/003/005/KIN	Open Label Multicenter	17.5, 35, or 70 µg/kg single dose	10	15	Investigator evaluation of hemostasis
F7HAEM/NAC/1/NAC	Open Label Multicenter	90 - 120 µg/kg every 2 hrs recommended	81	184	Investigator evaluation of hemostasis
MUL/VII/999/EMG-I MUL/VII/999/EMG-II	Open Label Multicenter	90 µg/kg every 2 hrs recommended	105	614	Patient and investigator evaluation of hemostasis
J/VII/015/TRE	Open Label Multicenter	40 - 100 µg/kg every 2-4 hrs recommended; mean dose 75 µg/kg	16	407	Patient and investigator evaluation of hemostasis

Table 7 – Efficacy Rates with rFVIIa in Congenital Hemophilia A/B Patients with Inhibitors

Patient Groups	Efficacy rate (%)	Reference
Patients during and immediately following elective surgery.	97 %	F7HAEM/USA/3/USA
Patients in the 48 hour post-operative period.	60-100 % *100% efficacy rate demonstrated in the 90 µg/kg dose group*	F7HAEM/USA/3/USA
Patients receiving treatment for joint or muscle or mucocutaneous bleeds at home.	95 %	F7HT/USA/1/USA
Patients treated for life-and limb-threatening bleeding. *The efficacy of **rFVIIa** has also been evaluated subsequent to the failure of other treatment modalities in the compassionate use program where efficacy rates of approximately 90% were observed for **rFVIIa** in controlling serious (CNS) bleeds and surgery.*	90 %	F7HAEM/USA/2/USA
Patients receiving treatment for primary joint, muscle and mucocutaneous bleeds in the hospital.	88 %	USA/VII/006/DOS-REV
Hemophilia A or B Patients with inhibitors undergoing elective major surgery. *Comparing i.v. bolus and i.v. continuous infusion of **rFVIIa**.*	75% for both treatment groups. *Based on the Global Hemostasis Treatment Evaluation for overall success in achieving and maintaining hemostasis at the end of the study period.*	HAEM-2011

Glanzmann's Thrombasthenia

Data were collected from the Glanzmann's Thrombasthenia Registry (GTR), the Hemostasis and Thrombosis Research Society (HTRS) registry, and the published literature.

From 2005 to 2011, the GTR captured data for 218 Glanzmann's thrombasthenia patients with 1073 bleeding and surgical events. An independent adjudication committee assessed clinical refractoriness, antibodies, and efficacy (two-point scale – success/failure) in 190 patients with 755 episodes requiring systemic hemostatic therapy (151 patients with 564 severe bleeding episodes, 90 patients with 192 surgeries). A total of 92 patients were treated with **NiaStase RT®** for 266 bleeding episodes and 77 patients treated for 160 surgical procedures. A large number of bleeding episodes were treated with **NiaStase RT®** alone (109/266 (41%) events).

The GTR was observational, and therefore not designed to select doses. The median dose of **NiaStase RT®** administered for bleeding episodes was 90 µg/kg (IQR: 90 to 95, range: 28 to 450); the median interval between doses was 3.0 hours (IQR: 2.0 to 6.0, range: 1 to 168). The median dose of **NiaStase RT®** administered for surgical procedures was 92 µg/kg (IQR 90 to 120, range: 4 to 270); the median interval between doses was 3.0 hours (IQR: 2.0 to 4.0, range: 1 to 749). The median dose administered for surgical procedures in patients with refractoriness with or without antibodies was 100 µg/kg (IQR: 90 to 140, range: 70 to 270). Concomitant use of other hemostatic agents occurred in 157/266 (59%) bleeding episodes and 94/160 (59%) surgical procedures.

In the GTR, **NiaStase RT®** was used in 43 children aged 0-12 years for 157 bleeding episodes and in 15 children aged 0-12 years for 19 surgical procedures. **NiaStase RT®** also was used in 8 children aged >12 to 16 years for 17 bleeding episodes and in 3 children aged >12 to 16 years for 3 surgical procedures. Efficacy of regimens including **NiaStase RT®** was evaluated by independent adjudicators as 93.6% and 100% for bleeding episodes in children aged 0-12 years and >12-16 years, respectively. Efficacy in surgical procedures was evaluated as 100% for all surgical procedures in children aged 0-16 years. No adverse reactions were reported in children.

The majority of **NiaStase RT®** treated surgical procedures were in adults (86%; >16 yrs.). Surgical procedures treated with **NiaStase RT®** included minor (134/160; 83.8%) and major (26/160, 16.3%) procedures; dental procedures were most commonly reported (106/160; 66.3%).

Overall, treatment with **NiaStase RT®** was successful in 94.4% of bleeding episodes (Table 8) and 99.4% of surgical procedures (Table 9). Adjudicator-rated efficacy was consistent across treatment regimens, bleed and surgery types, age, and refractory/antibody status. Treatment with **NiaStase RT®** was successful in patients with clinical refractoriness with or without platelet-specific antibodies in 94.9% of bleeding episodes and 98.6% of surgical procedures.

Table 8 - Adjudicator Evaluation of Efficacy – Bleeding Episodes

Treatment group	No. of patients[c]	No. of episodes	Success	Failure	Insufficient data	No Consensus
All NiaStase RT*	92	266	251 (94.4%)	4 (1.5%)	6 (2.3%)	5 (1.9%)
By Treatment Regimen						
NiaStase RT only	44	109	101 (92.7%)	2 (1.8%)	4 (3.7%)	2 (1.8%)
NiaStase RT ± Platelets ± Other hemostatic agents	69	157	150 (95.5%)	2 (1.3%)	2 (1.3%)	3 (1.9%)
By Antibody/Refractory Group						
Refractoriness ± Platelet-specific antibodies[a,d]	31	79	75 (94.9%)	2 (2.5%)	2 (2.5%)	0 (0.0%)
Platelet-specific-antibodies[a,d]	8	10	10 (100.0%)	0 (0.0%)	0 (0.0%)	NA
Neither/unknown[b,d]	57	177	166 (93.8%)	2 (1.1%)	4 (2.3%)	5 (2.8%)

*All treatment regimens that included treatment with **NiaStase RT®**

[a] includes GPIIb/IIIa, HLA, and unspecified platelet-specific antibodies

[b] Assumes no platelet-specific antibodies or refractoriness reported or antibody and refractory status unknown

[c] Patient numbers are not additive. Patients may have episodes with different treatment regimens and have more than one antibody/refractory status

[d] Treatment was **NiaStase RT®** only for 26/79 episodes with refractoriness with or without antibodies, 2/10 episodes with platelet specific antibodies only, and 81/177 episodes with neither or unknown. The remainder received **NiaStase RT®** with platelets and/or antifibrinolytic agents.

Table 9 - Adjudicator Evaluation of Efficacy – Surgical Procedures

Treatment group	No. of patients[c]	No. of proced.	Success	Insufficient data[e]
All NiaStase RT*	77	160	159 (99.4%)	1 (0.6%)
By Treatment Regimen				
NiaStase RT only	35	66	65 (98.5%)	1 (1.5%)
NiaStase RT ± Platelets ± Other hemostatic agents	57	94	94 (100.0%)	0 (0.0%)
By Antibody/Refractory Group				
Refractoriness ± Platelet-specific antibodies[a,d]	33	70	69 (98.6%)	1 (1.4%)
Platelet-specific antibodies[a,d]	11	24	24 (100.0%)	0 (0.0%)
Neither/unknown[b,d]	36	66	66 (100.0%)	0 (0.0%)

*All treatment regimens that included treatment with **NiaStase RT®**

[a] includes GPIIb/IIIa, HLA, and unspecified platelet-specific antibodies

[b] Assumes no platelet-specific antibodies or refractoriness reported or antibody and refractory status unknown

[c] Patient numbers are not additive. Patients may have episodes with different treatment regimens and have more than one antibody/refractory status

[d] Treatment was **NiaStase RT®** only for 22/70 episodes with refractoriness with or without antibodies, 13/24 episodes with platelet specific antibodies only, and 31/66 episodes with neither or unknown. The remainder received **NiaStase RT®** with platelets and/or antifibrinolytic agents.

[e] There were no reports of failure or lack of consensus captured in the database

In the HTRS, there were 7 patients that were treated with **NiaStase RT®** for 23 bleeding episodes. Concomitant hemostatic agents were administered for 11 episodes (antifibrinolytics in 10 episodes). Treatment was reported effective in 21 of 23 (91.3%) episodes. In the other 2 episodes, bleeding was reported as slowed or no improvement, however in neither episode was further treatment reported. There were no surgical procedures reported in the HTRS registry.

Information from the literature reports the use of **NiaStase RT®** in over 130 patients with Glanzmann's thrombasthenia.

Acquired Hemophilia Registries/Study

Data from patients with acquired hemophilia who were treated with **rFVIIa** were collected from the European Acquired Hemophilia (EACH2) Registry, the Hemostasis and Thrombosis Research Society (HTRS) Registry, and a Japanese Post-Marketing Surveillance Study (JPMS). These registries/study were observational and therefore not designed to select dose. Information pertaining to each registry/study and hemostatic outcomes is provided in Table 10 and Table 11 respectively.

Study Demographics and Study Design

Table 10 – Study Design and Efficacy Assessments for EACH2, HTRS and JPMS

Registry/ Study	Study Population	Treatment Regimen	Efficacy Assessments
EACH 2 Multicentre, pan-European, web-based database (2003-2008)	Patients with plasma FVIII activity <50 $UdL^{-1}$and detection of an inhibitor to FVIII. Patients with congenital hemophilia A or coagulation inhibitors other than anti-FVIII antibodies were excluded.	Control of bleeding episodes treated with a by-passing agent (**rFVIIa** or pd-aPCC), FVIII, or 1-desamino-8-D-arginine-vasopressin (DDAVP).	Hemostatic response for the first reported bleed only. Reported as "resolved/controlled" or "not resolved".
HTRS National patient registry to collect data (2004-2011)	Patients with congenital coagulation factor deficiencies, acquired inhibitors, platelet function disorders, von Willebrand disease, or patients treated with **rFVIIa**, irrespective of underlying bleeding disorder or inhibitor status. Patients with coagulation protein deficiencies due to liver failure or with thrombophilia were excluded.	No defined or recommended dose and regimen.	Hemostatic response reported after last **rFVIIa** dose. Reported as "bleeding stopped", "bleeding slowed but not stopped", or "no improvement".
JPMS Multicentre, non-	Patients with hemophilia A or B and inhibitors, including patients with acquired hemophilia.	No defined or recommended dose and regimen.	Hemostatic outcome graded into 4 categories. – Markedly effective: Clinical improvement within 8 hours. – Effective: Clinical improvement within 8-

interventional, observational study (2000-2010)			12 hours. – Moderately effective: Clinical improvement later than 12 hours or bleeds having improvement of less marked nature, irrespective of the time horizon. – Poor outcome: No clinical effects were observed at the time of evaluation.

Study Results

Treatment of Bleeding Episodes

A total of 589 bleeding episodes were evaluated after first-line treatment with **rFVIIa** in a total of 307 patients.

Table 11 – Hemostatic Outcomes – Bleeding Episodes

Registry/ Study	Number of Patients	Number of First-line Bleeds[d]	Dose Median (range)[e]	Findings	
				Hemostatic Outcome	**N (%)**
EACH2	159[a]	159	90.0 (18.5;1000.0)	Resolved/controlled	145 (91.2)
				Not resolved	14 (8.8)
HTRS	59[c]	128	90.0 (14.3;270.0)	Bleeding stopped	112 (87.5)
				Bleeding slowed but not stopped	13 (10.2)
				No improvement	3 (2.3)
JPMS	89[b]	302	93.2 (21.0;383.2)	Markedly effective	129 (42.7)
				Effective	26 (8.6)
				Moderately effective	120 (39.7)
				Poor outcome	27 (8.9)

[a] In the EACH2 registry1patient was under 16 years of age
[b] In the JPMS study 1patient was under 16 years of age
[c] In the HTRS registry no patients were under 16 years of age
[d] Interpreted as number of bleeds treated with **rFVIIa** monotherapy
[e] Dose per injection (µg/kg) listed with range covering minimum and maximum dose

Hemostatic Outcomes – Surgical Procedures

In the HTRS registry, 17 patients underwent 24 surgical procedures where **rFVIIa** was administrated prior and/or post-surgery. The median dose administered per injection was 91.6 µg/kg, with a range from 44.0 to 200.0 µg/kg (min; max). Outcome was reported for 23 of the 24 episodes. For 7 of the surgeries, transfusions were performed and/or concomitant hemostatic medication was administered. The majority of the surgeries, 74% (17/23), reported hemostatic outcome as "excellent/good". Most of the surgeries were considered to be minor.

Information in the surgical setting was also collected from clinical studies from the Novo Nordisk compassionate use program. The median of the average dose administered per injection was 89.1 µg/kg, with a range from 30.8 to 197.4 µg/kg (min; max). For 10 of the surgeries, transfusions were performed and/or concomitant hemostatic medication was administered. Treatment with **rFVIIa** was determined to be effective or partially effective in 87% (27/31) of bleeding episodes for which efficacy data were available, and ineffective in 13% (4/31) of episodes. Outcome was not reported for one episode. Most of the surgeries were considered to be minor.

Additional data from the literature suggest the efficacy of **rFVIIa** to treat or prevent bleeding during/following a number of surgical procedures including major surgeries. However, other concomitant medications were sometimes used.

Congenital Factor VII Deficiency

Data from patients with congenital Factor VII deficiency who were treated with **rFVIIa** were collected from the Seven Treatment Evaluation Registry (STER). The STER registry was not designed to select dose.

A total of 162 patients receiving **rFVIIa**, with or without hemostatic concomitant medication, were enrolled in the STER registry. Of these, 59 patients had bleeding episodes, 101 patients underwent surgery and 29 patients were given **rFVIIa** as prophylactic treatment. Several patients had more than one admission and also different types of admissions (i.e. bleeding episode, surgery or prophylactic treatment). Overall, an equal number of male and female patients were enrolled (48% and 52%, respectively). The mean age was 28 years.

Study Demographics and Study Design

Table 12 – Study Design and Efficacy Assessments for STER for the Treatment of Bleeding Episodes

Registry/ Study	Study Population	Treatment Regimen	Efficacy Assessments
STER Registry Prospective, observational, international, multi-centre study	Male and female patients with congenital FVII deficiency (defined as plasma levels of FVII < 50% of normal or a mutation known to be associated with FVII deficiency) for whom treatment of acute bleeding episodes, prevention of bleeding during surgery/delivery and primary/secondary prophylaxis was considered necessary by the treating physician.	Dosed according to local treatment practice. • Doses of 15−30 µg/kg every 4 to 6 hours until hemostasis was achieved for both on- demand treatment and for prevention of bleeding in surgery or invasive procedures. Dose and frequency of injections were adapted to each individual patient.	***Efficacy in treatment of bleeding episodes (6-hour evaluation)*** Response to treatment of bleeding episodes was evaluated 6 hours after treatment according to the following scale: • Excellent: – Single dose administration leading to a cessation of overt bleeding and of symptoms related to the bleeding episode – Prompt (within a few hours) relief of pain – Stop of swelling • Effective: – When more than one dose administration was needed to obtain results evaluated as excellent • Partially effective: – When more than one dose administration was needed, but symptoms subside slowly • Ineffective: – When there are no changes in bleeding pattern • Not evaluable ***Efficacy in surgery*** Perioperative treatment effect was evaluated during surgery according to the following scale: • Good: – No bleeding • Partially effective: – Minor hematomas and loss of blood through drainages • Ineffective • Not evaluable

Study Results

Treatment of Bleeding Episodes

A total of 59 patients (33 females and 26 males) receiving **rFVIIa** with or without hemostatic concomitant medication had a total of 91 bleeding episodes. Of the 71 bleeding episodes with a registered cause of the bleed, 76.1% were spontaneous and 23.9% were traumatic. The 91 bleeding episodes were registered in 111 locations, and some bleeding episodes were registered with more than one location. The majority of bleeding episodes were hemarthrosis (27.9%), epistaxis (18.9%), menorrhagia (13.5%) and gum bleeding (12.6%).

A summary of efficacy evaluated at 6 hours post-dosing is presented by treatment regimen in Table 13.

Table 13 – Summary of Efficacy Evaluations at 6 hours of Bleeding Episodes by Treatment Regimen

	Spontaneous	**Traumatic**	**Missing cause**	**Total**
	N (%)	**N (%)**	**N (%)**	**N (%)**
All				
No. of subjects	29	15	20	59
N*	54	16	19	89
Excellent	39 (72.2)	9 (56.3)	5 (26.3)	53 (59.6)
Effective	12 (22.2)	6 (37.5)	10 (52.6)	28 (31.5)
Partially effective	2 (3.7)	-	4 (21.1)	6 (6.7)
Ineffective	-	-	-	-
Not evaluable	1 (1.9)	1 (6.3)	-	2 (2.2)
By Treatment Regimen				
NiaStase RT® monotherapy				
No. of subjects	19	14	12	43
N*	40	15	12	67
Excellent	32 (80.0)	8 (53.3)	4 (33.3)	44 (65.7)
Effective	6 (15.0)	6 (40.0)	6 (50.0)	18 (26.9)
Partially effective	1 (2.5)	-	2 (16.7)	3 (4.5)
Ineffective	-	-	-	-
Not evaluable	1 (2.5)	1 (6.7)	-	2 (3.0)
NiaStase RT® with hemostatic concomitant medication **				
No. of subjects	10	1	8	18
N*	10	1	7	18
Excellent	5 (50.0)	1 (100.0)	1 (14.3)	7 (38.9)
Effective	4 (40.0)	-	4 (57.1)	8 (44.4)
Partially effective	1 (10.0)	-	2 (28.6)	3 (16.7)
Ineffective	-	-	-	-
Not evaluable	-	-	-	-

* N: number of bleeds with non-missing efficacy response. 2 bleeds had missing efficacy response. One was a traumatic bleed treated with **NiaStase RT®** monotherapy; the other had missing cause and was treated with **NiaStase RT®** and concomitant hemostatic medication. A subject could have more than one bleed, and therefore the number of subjects in each group does not sum to the total.

** Hemostatic concomitant medications: Tranexamic acid, Amicar, Fresh frozen plasma and Packed Red.

Overall, the mean number of doses used for treatment of bleeding episodes was 4.9 (range: 1 to 87). The mean and median dose per injection used for treatment of bleeding episodes was 33.8 μg/kg and 30.0 μg/kg, respectively (range: 3.8 to 160 μg/kg).

Surgery

All surgeries in the STER registry have been classified as minor or major surgeries post-hoc. A major surgery was defined as any surgical procedure (elective or emergent) that usually involved general anesthesia and/or respiratory assistance and in which a major body cavity was penetrated and exposed or a substantial impairment of physical or physiological functions was produced (e.g., laparotomy, thoracotomy, craniotomy). A minor surgery was defined as any surgical procedure (elective or emergent) that did not involve general anesthesia and/or respiratory assistance (e.g., minor dental extractions, incision, and drainage of abscess, or simple excisions).

A total of 101 patients (54 females and 47 males) receiving **rFVIIa** with or without hemostatic concomitant medication underwent a total of 118 surgeries. Of these 118 surgeries, 74 (62.7 %) were major and 44 (37.3 %) were minor. In 19 out of 118 (16.1%) surgeries blood loss was registered. In the patients who experienced blood loss, the mean loss was 316 mL (range: 2−1800 mL) and the median blood loss was 100 mL. RBC was administered during 9 surgeries and the mean and median number of RBC units given was 2 (range: 1−4 units). A summary of treatment efficacy for surgeries is shown in Table 14.

Table 14 – Summary of Efficacy Evaluations for Surgeries by Treatment Regimen

	Major	**Minor**	**Total**
	N (%)	**N (%)**	**N (%)**
All			
No. of subjects	64	42	101
N*	74	44	118
Good	69 (93.2)	43 (97.7)	112 (94.9)
Partially effective	2 (2.7)	-	2 (1.7)
Ineffective	-	-	-
Not evaluable	3 (4.1)	1 (2.3)	4 (3.4)
By Treatment Regimen			
NiaStase RT® monotherapy			
No. of subjects	40	29	67
N*	45	30	75
Good	41 (91.1)	29 (96.7)	70 (93.3)
Partially effective	1 (2.2)	-	1 (1.3)
Ineffective	-	-	-
Not evaluable	3 (6.7)	1 (3.3)	4 (5.3)
NiaStase RT® with hemostatic concomitant medication*			
No. of subjects	17	11	27
N*	19	12	31
Good	19 (100.0)	12 (100.0)	31 (100.0)
Partially effective	-	-	-

Ineffective	-	-	-
Not evaluable	-	-	-

* N: Number of surgeries with non-missing efficacy assessments. All surgeries had an efficacy response. A subject could have more than one bleed, and therefore the number of subjects in each group does not sum to the total.
** Hemostatic concomitant medications: Tranexamic acid, Fiblin glue- beriplast and Fresh frozen plasma.

A mean dose of 29.1 µg/kg **rFVIIa** (range: 0.6−300 µg/kg) was administered during surgery. The mean accumulated dose was 190.1 µg/kg (range: 7.2−9720 µg/kg). On average **rFVIIa** was given as 6.5 doses (range: 1−122 doses) and was administered over 2.8 treatment days (range: 1−20 days).

Comparative Bioavailability Studies

Trial NN1007-1744 was a single-centre, randomised, double-blind, two-way cross-over trial investigating the bioequivalence of **NiaStase®** (the marketed formulation of rFVIIa) and **NiaStase RT®** (the room temperature stable formulation of rFVIIa) in healthy male subjects. The primary objective was to prove the hypothesis of bioequivalence (based on AUC) between **NiaStase®** and **NiaStase RT®**. Secondary objectives were to compare the rFVIIa pharmacokinetic parameters and to investigate the short term safety and tolerability of **NiaStase RT®** including injection site tolerability and antibody formation.

A total of 25 healthy Caucasian males, between 22 and 44 years of age, were randomised to receive a single i.v. dose of 90 µg/kg of both formulations in random order, separated by a washout period of 2-3 weeks. A total of 22 of the 25 dosed subjects were included in the pharmacokinetic analyses. The pharmacokinetic parameters were calculated using non-compartmental methods. An analysis of variance (ANOVA) was performed and a 90% two-sided confidence interval for the ratio (**NiaStase RT®**/ **NiaStase®**) was calculated. Bioequivalence was claimed if the two-sided 90% interval was completely within the interval [0.80-1.25].

The two rFVIIa formulations had similar plasma profiles and pharmacokinetic parameters. Bioequivalence between the two formulations was concluded based on AUC, as the 90% confidence interval was included within the predefined range 0.80-1.25 (see Table 15).

Table 15 - Mean Values and 90% Confidence Interval for the Ratio of NiaStase RT®/ NiaStase® of Pharmacokinetic Parameters

NiaStase RT® (90 µg/kg) From measured data[a]				
Parameter	**NiaStase RT® (Test)**	**NiaStase® (Reference)**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T[b], h*IU/mL	112.36	120.18	93.5	[90.0 ; 97.1]
AUC_I[b], h*IU/mL	112.37	120.19	93.5	[90.0 ; 97.1]
C_{MAX}[b], IU/mL	52.77	54.86	96.2	[93.1 ; 99.3]
T_{MAX}[c,d], hours	0.08 (NA.)	0.08 (NA.)		
$T_{½}$[c], hours	3.56 (0.079)	3.48 (0.079)		

a: The results in this table are based on the completers
b: geometric mean
c: arithmetic mean (CV %)
d: Following i.v. administration there is no absorption phase and the T_{Max} was predefined as 5 minutes.

DETAILED PHARMACOLOGY

A hemophilia rat model is not available. In this species, the direct effect of eptacog alfa, activated (**rFVIIa**) on bleeding was studied in warfarin-treated rats in a rat tail bleeding test. Warfarin treatment results in low levels of the vitamin K-dependent coagulation factors such as Factor II (prothrombin) and X which are essential for the effect of FVIIa. The effect of **rFVIIa** on prothrombin time in rat plasma was determined, where thromboplastin was prepared from rat brain. Similar tests were conducted in rabbits. The hemostatic effect of **rFVIIa** was studied in hemophiliac dogs, which are considered the standard model.

- The increased bleeding time in warfarin-treated rats was completely normalized by **rFVIIa** 195 µg/kg and partially normalized by 39 µg/kg. This was associated with normalization of prothrombin time, and a modest reduction of activated partial thromboplastin time.

- In warfarin-treated rats, **rFVIIa** 13 or 40 µg/kg almost normalized prothrombin time; shortening of activated partial thromboplastin time was modest. Similar results were obtained in rabbits.

- **rFVIIa** corrects the hemostatic defect in hemophilia A and B dogs both when given as prevention, i.e. before the onset of bleeding, and when given as treatment of ongoing bleeding (45-155 µg/kg, single dose).

A study in rabbits examining coagulation following administration of 78 to 780 µg/kg **rFVIIa** alone, 50 U/kg of an activated prothrombin complex concentrate (aPCC) alone, or a combination of **rFVIIa** and the aPCC was performed. The results demonstrated decreased platelets and fibrinogen and increased activated partial thromboplastin time (aPTT) subsequent to a PCC administration and no effect following **rFVIIa** administration. Administration of 50 U/kg aPCC and then 78 µg/kg **rFVIIa** within 5 minutes demonstrated a trend towards increased coagulation

factor consumption effects beyond those levels observed with aPCC administration alone. During the clinical program, 4 episodes of clinical or laboratory evidence of DIC were documented in hemophilia patients with inhibitors.

A study in rabbits examining coagulation following administration of 100 µg/kg **rFVIIa** in combination with tranexamic acid demonstrated no interaction effect on coagulation parameters.

TOXICOLOGY

Carcinogenesis and Mutagenesis, Impairment Fertility

Two mutagenicity studies have given no indication of carcinogenic potential for **rFVIIa**. The clastogenic activity of **rFVIIa** was evaluated in both *in vitro* studies (i.e. cultured human lymphocytes) and *in vivo* studies (i.e. mouse micronucleus test). Neither of these studies indicated clastogenic activity of **rFVIIa**. Gene mutation studies (e.g. Ames test) have not been performed with **rFVIIa**. No chronic carcinogenicity studies have been performed with **rFVIIa**.

Preclinical reproductive studies in male and female rats with dose ranges of 0.33-6.0 mg/kg/day had no effect on mating performance, fertility or litter characteristics.

Acute toxicity

- No drug-related effects were seen in mice at doses of 0.24 to 3.9 mg/kg. In other studies, mice treated at 0.69 to 14.8 mg/kg showed decreased activity, unsteady gait, convulsions, and laboured respiration.
- At 15.6 mg/kg in mice, clinical signs were seen on day of dosing only; they included laboured and rapid respiration, ptosis, piloerection, decreased rectal temperature, decreased activity. There were some deaths, in some cases preceded by convulsions.
- Histopathology of mice revealed edema at the injection site (treated and controls), the presence of occlusions or fibrin emboli of the large vessels of the lungs caused by intravascular coagulation.
- No drug-related toxicity in rats at doses of up to 15.6 mg/kg. Discolouration of the injection site seen at the higher doses.

Long Term Toxicity

Table 16 – Long Term Toxicity Studies in Animals

Animal Species			
Rat	No drug-related effects seen in rats treated with up to 0.86 mg/kg/day (28 days), or 0.33 mg/kg/day (13 weeks). At 4.3 mg/kg/day necrosis at injection site, decreased weight gain and food consumption were attributed to treatment. At the higher doses, changes which were an expression of the pharmacological effect were seen, including: hematological changes, thrombus formation and emboli. There were deaths.	Antibodies against **rFVIIa** were present. There was a dose-dependant increase in clotting activity.	
Dog	No drug-related effects seen in dogs treated with up to 0.62 mg/kg/day (7 day treatment). Treatment for 2 additional days with 1.33 mg/kg/day caused anaphylactic shock.	Antibodies against **rFVIIa** were present.	
Monkey	At 15 mg/kg/day toxicity was observed; this led to the female being sacrificed. Antibodies against **rFVIIa** were present.	No clinical observations when treated at 2.3 mg/kg/day for 28 days, or 3 mg/kg/day for 13 weeks. In the lung, in a small proportion of the vasculature, there were foci of intimal proliferation, and occasional thrombosis in some animals treated with 2.3 mg/kg/day.	Animals developed antibodies against **rFVIIa**. There was a dose-dependent increase in FVII clotting activity.

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IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

NiaStase RT®
(eptacog alfa, activated)
Activated Recombinant Human Blood Coagulation
Factor VII Room Temperature Stable

This leaflet is Part III of a three-part 'Product Monograph' published when **NiaStase RT®** was approved for sale in Canada and designed specifically for Consumers. This leaflet is a summary and will not tell you everything about **NiaStase RT®**. Contact your doctor or Hemophilia Care Centre if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for

NiaStase RT® or eptacog alfa (activated) is more commonly known as activated recombinant human blood coagulation Factor VII (rFVIIa). **NiaStase RT®** is a clotting factor produced using recombinant DNA technology. **NiaStase RT®** or rFVIIa is free of all human plasma components, eliminating any possibility of contamination through the blood.

NiaStase RT® is used:

- In hemophilia A and hemophilia B patients with inhibitors to FVIII or FIX, respectively, for the treatment of bleeding episodes (including treatment and prevention of those occurring during and after surgery).
- To treat bleeding episodes, or prevent bleeds during surgery, in patients with Glanzmann's thrombasthenia (a bleeding disorder) when platelet transfusions are no longer effective or when platelets are not available.
- In adult patients with acquired hemophilia, for the treatment of bleeding episodes, and for the prevention of bleeding in those undergoing surgery or invasive procedures.
- In patients with congenital Factor VII deficiency, for the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures.

What it does

NiaStase RT® is a medicine that works by activating the clotting system in the blood at the site of bleeding to prevent or eliminate the bleeding.

When it should not be used

Pregnancy and breastfeeding
Remember to tell your doctor or nurse if you are pregnant or are breastfeeding. Women of child-bearing potential should avoid becoming pregnant during treatment. Nursing mothers should discontinue nursing during treatment.

DO NOT use **NiaStase RT®** with any other clotting products. However, your doctor may prescribe other therapies to be used at the same time as **NiaStase RT®**.

What the medicinal ingredient is

Eptacog alfa, activated, contains activated recombinant human blood coagulation Factor VII (rFVIIa), which is similar to the natural human clotting Factor VIIa.

What the nonmedicinal ingredients are

NiaStase RT® contains the following nonmedicinal ingredients: calcium chloride dihydrate, glycylglycine, mannitol, methionine, polysorbate 80, sodium chloride and sucrose.

The solvent for reconstitution that comes with **NiaStase RT®** contains histidine in water for injections.

What dosage forms it comes in

NiaStase RT® comes as a freeze-dried powder available in 1.0 mg (50 KIU), 2.0 mg (100 KIU), 5.0 mg (250 KIU), and 8.0 mg (400 KIU) vials. The freeze-dried powder in a vial is reconstituted (dissolved) with the histidine solvent that is supplied with your **NiaStase RT®**.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- The extent of the risk of developing blood clots after using **NiaStase RT®** is not known but is considered to be low. You may have an increased risk of developing blood clots if you have experienced a crush injury, have infection of the blood, hardening of the arteries or if you are prone to develop blood clots. If so, contact your Hemophilia Care Centre or doctor.
- Patients that lack the blood clotting factor VII (known as factor VII deficiency) can have an allergic response to **NiaStase RT®**.

BEFORE you use **NiaStase RT®** talk to your doctor if:

- you have experienced a crush injury;
- you have infection of the blood;
- you have hardening of the arteries;
- you are prone to develop blood clots.

*This information will help your doctor and you decide whether you should use **NiaStase RT®** and what extra care may need to be taken while you are on the medication.*

INTERACTIONS WITH THIS MEDICATION

Tell your doctor if you are taking, have recently taken or might take any other medicines.

Do not use **NiaStase RT®** at the same time as prothrombin complex concentrates or recombinant Factor XIII.

You should talk to your doctor before using **NiaStase RT®** if you also use Factor VIII or IX products.

There is limited experience of using **NiaStase RT®** together with medicines called antifibrinolytic drugs (such as tranexamic acid) which are also used to control bleeding. You should talk to your doctor before using **NiaStase RT®** with these medicines.

Interactions with other drugs have not been established.

Before using **NiaStase RT®**, talk to your doctor about any medicine you use.

PROPER USE OF THIS MEDICATION

NiaStase RT® is available in four different strengths. Always check that you have the strength prescribed by your doctor. Always use an aseptic technique when injecting **NiaStase RT®**.

For instructions on how to prepare and administer **NiaStase RT®** please refer to the end of this leaflet.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

*Unwanted effects are possible with all medicines. Tell your Hemophilia Care Centre or doctor as soon as possible if you do not feel well while you are receiving treatment with **NiaStase RT®**.*

You may experience some redness at the injection site. This is normal. However, if you develop more severe symptoms such as: hives, itching, tightness of the chest, wheezing, or any other unusual effects, you should contact your Hemophilia Care Centre or doctor **immediately**.

Isolated cases of hypersensitivity reactions including anaphylactic reactions have been reported. Remind your doctor if you have a history of allergic reactions as you may need to be monitored more carefully.

Seek medical attention without delay, if bleeding does not appear to be adequately responding to treatment.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom/effect		**Talk with your doctor or Hemophilia Care Centre**		**Stop taking drug and call your doctor**
		Only if severe	**In all cases**	
Common	Redness at injection site	✓		
Uncommon	Hives		✓	
	Itching		✓	
	Tightness of chest			✓
	Wheezing			✓
	Unusual effects		✓	
	If bleeding does not stop		✓	

*This is not a complete list of side effects. For any unexpected effects while taking **NiaStase RT®**, contact your doctor.*

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE IT

Prior to reconstitution, keep **NiaStase RT®** powder and histidine solvent refrigerated or store between 2° to 25°C. Do not freeze. Protect powder and solvent from light. Do not use past the expiration date on the label.

After reconstitution, **NiaStase RT®** should be used immediately. If you do not use immediately after mixing, **NiaStase RT®** may be stored at room temperature (below 25°C) for no longer than 6 hours or refrigerated at 2°C to 8°C for no longer than 24 hours. Do not freeze or store reconstituted **NiaStase RT®** in syringes.

Keep all medication and supplies out of the reach of children.

MORE INFORMATION

If you still have questions or would like more information, please contact your doctor or Hemophilia Care Centre.

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.novonordisk.ca or by contacting Novo Nordisk Canada Inc., at: 1-800-465-4334

This leaflet was prepared by Novo Nordisk Canada Inc.

Last revised: October 18, 2018

Reconstitution and Administration Instructions using Prefilled Syringe with Solvent (MixPro®)

INSTRUCTIONS ON HOW TO USE NIASTASE RT®

READ THESE INSTRUCTIONS CAREFULLY BEFORE USING NIASTASE RT®.

NiaStase RT® is supplied as a powder. Before injection (administration) it must be reconstituted (mixed) with the solvent supplied in the syringe. The solvent is a histidine solution.

Do not mix NiaStase RT® with any other intravenous infusions or medications.

The reconstituted **NiaStase RT®** must be injected into your vein (intravenous injection). The equipment in this package is designed to reconstitute and inject **NiaStase RT®**.

You will also need an infusion set (tubing and butterfly needle), sterile alcohol swabs, gauze pads and plasters. These devices are not included in the **NiaStase RT®** package.

Do not use the equipment without proper training from your doctor or nurse.

Always wash your hands and ensure that the area around you is clean.

When you prepare and inject medication directly into the vein, it is important to **use a clean and germ free (aseptic) technique.** Improper technique can introduce germs that can infect the blood.

Do not open the equipment until you are ready to use it.

Do not use the equipment if it has been dropped, or if it is damaged. Use a new package instead.

Do not use the equipment if it is expired. Use a new package instead. The expiry date is printed on the outer carton, on the vial, on the vial adapter, and on the prefilled syringe.

Do not use the equipment if you suspect it is contaminated. Use a new package instead.

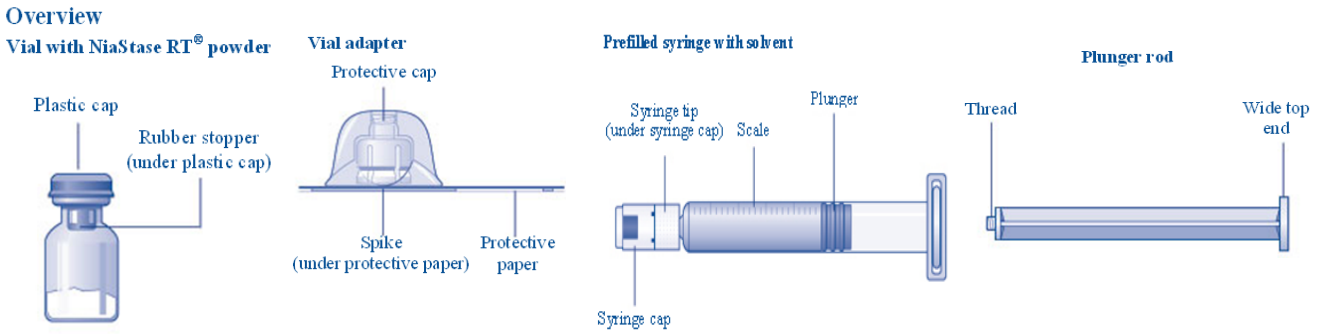
Do not dispose of any of the items until after you have injected the reconstituted solution.

The equipment is for single use only.

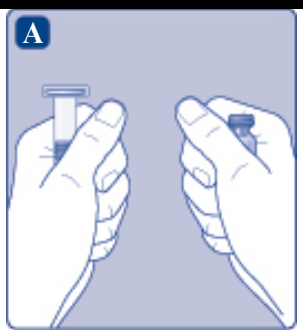
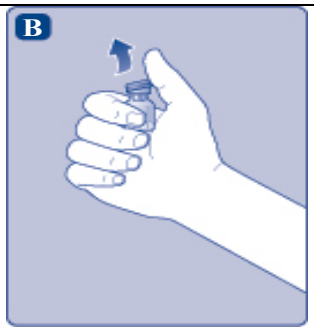
Contents

The package contains:
• 1 vial with **NiaStase RT®** powder
• 1 vial adapter
• 1 prefilled syringe with solvent
• 1 plunger rod (placed under the syringe)

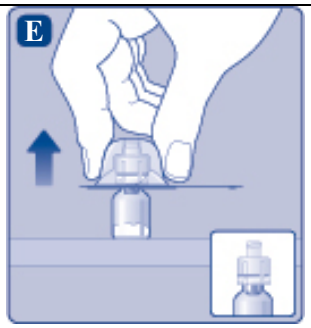
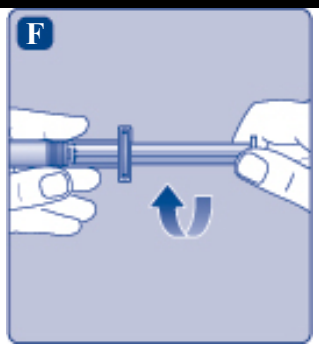
The prefilled solvent syringe with sterile vial adapter, together serve as a needleless reconstitution system named the MixPro®.

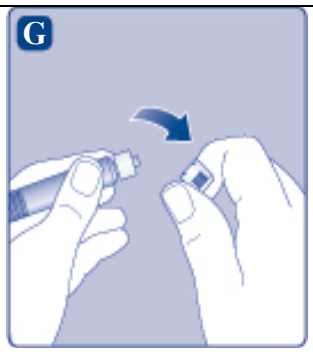
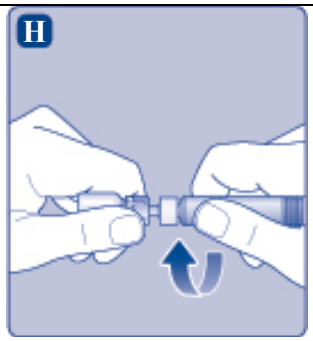
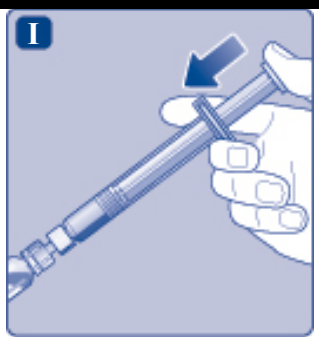
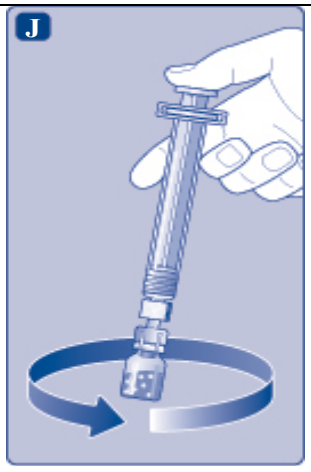


1. Prepare the Vial and Syringe

Step A		**Take out the number of NiaStase RT® packages you need.** **Check the expiry date.** **Check the name, strength and colour** of the package, to make sure it contains the correct product. **Wash your hands** and dry them properly using a clean towel or air dry. Take the vial, the vial adapter and the prefilled syringe out of the carton. **Leave the plunger rod untouched in the carton.** **Bring the vial and the prefilled syringe to room temperature** (not above 37°C). You can do this by holding them in your hands until they feel as warm as your hands. **Do not use any other way to warm** the vial and prefilled syringe.
Step B		**Remove the plastic cap** from the vial. **If the plastic cap is loose or missing, do not use the vial.** **Wipe the rubber stopper** with a sterile alcohol swab and allow it to air dry for a few seconds before use to ensure that it is as germ free as possible. **Do not touch the rubber stopper with your fingers as this can transfer germs.**

2. Attach the Vial Adapter

Step C		**Remove the protective paper** from the vial adapter. **If the protective paper is not fully sealed or if it is broken, do not use the vial adapter.** **Do not take the vial adapter out of the protective cap with your fingers.** If you touch the spike on the vial adapter germs from your fingers can be transferred.
Step D		**Place the vial on a flat and solid surface.** **Turn over the protective cap,** and snap the vial adapter onto the vial. **Once attached, do not remove the vial adapter from the vial.**
Step E		Lightly **squeeze the protective cap** with your thumb and index finger as shown. **Remove the protective cap** from the vial adapter. **Do not lift the vial adapter from the vial** when removing the protective cap.
3. Attach the Plunger Rod and the Syringe		
Step F		Grasp the plunger rod by the wide top-end and take it out of the carton. **Do not touch the sides or the thread of the plunger rod.** If you touch the sides or the thread, germs from your fingers can be transferred**.** **Immediately** connect the plunger rod to the syringe by turning it clockwise into the plunger inside the prefilled syringe until resistance is felt.

Step G		**Remove the syringe cap** from the prefilled syringe by bending it down until the perforation breaks. **Do not touch the syringe tip under the syringe cap.** If you touch the syringe tip, germs from your fingers can be transferred. **If the syringe cap is loose or missing, do not use the prefilled syringe.**
Step H		**Screw the prefilled syringe securely** onto the vial adapter until resistance is felt.
4. Reconstitute the Powder with the Solvent		
Step I		**Hold the prefilled syringe slightly tilted** with the vial pointing downwards. **Push the plunger rod** to inject all the solvent into the vial.
Step J		**Keep the plunger rod pressed down and swirl** the vial gently until all the powder is dissolved. **Do not shake the vial as this will cause foaming.** **Check the reconstituted solution.** It must be colourless. **If you notice visible particles or discoloration, do not use it.** Use a new package instead.
NiaStase RT® is recommended to be used immediately after it has been reconstituted. This is because if left, the		

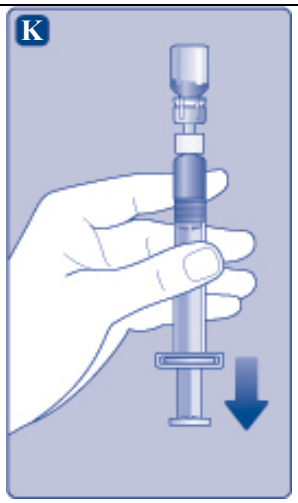
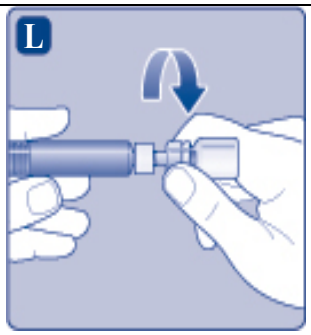
medicine may no longer be sterile and could cause infections.

If you cannot use the reconstituted NiaStase RT® solution immediately, it should be kept in the vial (with the vial adapter and the syringe still attached) and stored at room temperature (below 25°C) for no longer than 6 hours or refrigerated (2°C to 8°C) for no longer than 24 hours.

Do not freeze reconstituted NiaStase RT® solution or store it in syringes.

Keep reconstituted NiaStase RT® solution out of direct light.

(I)
If your dose requires more than one vial, repeat steps A to J with additional vials, vial adapters and prefilled syringes until you have reached your required dose.

Step K		**Keep the plunger rod pushed completely in.** **Turn the syringe** with the vial upside down. **Stop pushing the plunger rod and let it move back** on its own while the reconstituted solution fills the syringe. **Pull the plunger rod slightly downwards** to draw the reconstituted solution into the syringe. In case you only need part of the reconstituted solution, use the scale on the syringe to see how much of the solution you withdraw, as instructed by your doctor or nurse. If, at any point, there is too much air in the syringe, inject the air back into the vial. While holding the vial upside down, **tap the syringe gently** to let any air bubbles rise to the top. **Push the plunger rod** slowly until all air bubbles are gone.
Step L		**Unscrew the vial adapter** with the vial. **Do not touch the syringe tip.** If you touch the syringe tip, germs from your fingers can be transferred.

<u>Injecting NiaStase RT® with prefilled syringe (MixPro®) via needleless connectors for intravenous (IV) catheters</u>

Caution: The MixPro® prefilled solvent syringe is made of glass and is designed to be compatible with standard luer-lock connections. Some needleless connectors with an internal spike are incompatible with the prefilled syringe. This incompatibility may prevent administration of the drug and/or result in damage to the needleless connector.

Follow the instructions for use that come with the needleless connector. Administration through a needleless connector may require withdrawal of the reconstituted solution into a standard 10 mL sterile luer-lock plastic syringe. This should be done right after Step J.

If you have encountered any problems with attaching the prefilled histidine solvent syringe to any luer-lock compatible device, or have any questions please contact Novo Nordisk at 1-800-465-4334.

5. Inject the Reconstituted Solution

NiaStase RT® is now ready to inject into your vein.

Inject the reconstituted solution as instructed by your doctor or nurse.

Inject slowly over 2 to 5 minutes.

Injecting the solution via a central venous access device (CVAD) such as a central venous catheter or a subcutaneous port:

- Use a clean and germ free (aseptic) technique. Follow the instructions for proper use for your connector and CVAD in consultation with your doctor or nurse.
- Injecting into a CVAD may require using a sterile 10 mL plastic syringe for withdrawal of the reconstituted solution.
- If the CVAD line needs to be flushed before or after **NiaStase RT®** injection, use 0.9% Sodium Chloride solution for injection.

6. Disposal

Step M		**After injection, safely dispose** of the syringe with the infusion set, the vial with the vial adapter, any unused **NiaStase RT®** and other waste materials as instructed by your doctor or nurse. Do not throw it out with the ordinary household waste.

Do not disassemble the equipment before disposal.

Do no reuse the equipment.