PRODUCT MONOGRAPH

Schedule D

NiaStase®

eptacog alfa (activated)
activated recombinant human blood coagulation Factor VII

Lyophilized Powder

1.2 mg per vial (60 KIU/vial)
2.4 mg per vial (120 KIU/vial)
4.8 mg per vial (240 KIU/vial)

Professed

Coagulation Factor

Novo Nordisk Canada Inc.
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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/ 1.2 mg (60 KIU) 2.4 mg (120 KIU) 4.8 mg (240 KIU)	calcium chloride dihydrate, glycylglycine, mannitol, polysorbate 80, sodium chloride *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

DESCRIPTION

NiaStase® (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® (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 **NiaStase®** in the treatment of hemophilia patients with inhibitors, the apparent lack of anamnestic response during and after exposure to **NiaStase®** makes it suitable for use in all inhibitor patients.

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®**.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Both arterial and venous thromboembolic adverse events have been reported after treatment with **NiaStase®**, mostly in patients with predisposing concurrent risk factors. (See *General* under WARNINGS AND PRECAUTIONS; Pharmacodynamics, under ACTION AND CLINICAL PHARMACOLOGY; ADVERSE REACTIONS).
- Patients with inherent Factor VII deficiency may have pre-existing or may develop anti-Factor VII antibodies during therapy with **NiaStase®**. 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 **NiaStase®** (eptacog alfa, activated) 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 the risk of thromboembolic complications, caution should be exercised when administering **NiaStase®** 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®** should be weighed against the risk of these complications.

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

Patients who receive **NiaStase®** 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 rFVIIa dosage should be reduced or treatment stopped, depending on the patient's symptoms.

Patients self-administering **NiaStase**® 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**® 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 **NiaStase**®. Initial treatment with **NiaStase**® 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 recombinant coagulation factor VIIa, **NiaStase**®, 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 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.

A special package insert ***'Consumer Information'*** for patients who self-administer **NiaStase**® in a home setting is provided in each package. Also provided in the same package are instructions entitled, ***'Health Professional Information'***.

Carcinogenesis and Mutagenesis

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

Special Populations

Pregnant Women:
As a precautionary measure it is preferable to avoid the use of **NiaStase®** 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 **NiaStase®** 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®** should be made taking into account the benefit of breast-feeding to the child and the benefit of **NiaStase®** therapy to the woman.

Pediatric Patients (birth to 16 years of age):
Evidence for the safety and effectiveness of **NiaStase®** 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 **NiaStase®** 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 also PART II - CLINICAL TRIALS.

Geriatric Patients (≥ 65 years of age):
Clinical studies in hemophilia did not enrol geriatric patients.

Monitoring and Laboratory Tests

It should be noted that the therapeutic range of **NiaStase®** 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®** in patients.

Monitoring the effectiveness of therapy, the need for additional doses of **NiaStase®** 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**® therapy. Severity of bleeding condition and clinical response to **NiaStase**® administration must guide dosing requirements.

After administration of **NiaStase**®, 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 **NiaStase**®.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most serious adverse drug reactions observed in patient receiving **NiaStase**® (eptacog alfa, activated) are thrombotic events, however the extent of the risk of thrombotic adverse events after treatment with **NiaStase**® in individuals with hemophilia and inhibitors is considered to be low.

The most common adverse drug reactions observed for the labelled indication of **NiaStase**® are pyrexia, injection site reaction, headache, hypertension, hypotension, nausea, vomiting, pain, oedema and rash. See WARNINGS AND PRECAUTIONS.

Patients who receive **NiaStase**® 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 the Hemophiliac Population

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 **NiaStase**®. 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 **NiaStase®** (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 **NiaStase®**, 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 **NiaStase®**.

No severe allergic reactions have occurred in hemophilia patients receiving **NiaStase®**. Additionally, the potential for development of antibodies towards **NiaStase®** has been followed in hemophilia A/B patients and in none of these cases have antibodies towards **NiaStase®** 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 **NiaStase®** 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 NiaStase® Treatment Episodes and were considered to be possibly related to NiaStase® 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%)

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

Table 2 – Coagulation Parameter Shifts in Hemophilia A/B Patients with Inhibitors

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 in Hemophilia A/B Patients with Inhibitors

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
Creatine	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 creatine may indicate renal function changes.

Post-Market Adverse Drug Reactions

The following 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.

Based on post-marketing experience adverse drug reactions are rare (< 1 per 1,000 standard doses). When analyzed by system organ classes, the reporting rates of adverse drug reactions during the post-marketing period, 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	
Very rare (<1/10,000)	- Disseminated intravascular coagulation - Coagulopathy
Gastrointestinal disorders	
Very rare (<1/10,000)	- Nausea - Vomiting
General disorders and administration site conditions	
Rare (> 1/10,000, <1/1,000)	- Therapeutic response decreased* - Pyrexia - Injection site reaction including bruising and swelling *Lack of efficacy (therapeutic response decreased) has been reported. It is important that the dosage regimen of **NiaStase**® is compliant with the recommended dosage as stated. See DOSAGE AND ADMINISTRATION.
Immune system disorders	
Very rare (<1/10,000)	- Immune mediated reactions including anaphylactic reaction, and hypersensitivity
Investigations	
Very rare (<1/10,000)	- Fibrin D-dimer increased - Thrombin-antithrombin III complex increased - Increased troponin I and troponin T - Anti FVII antibodies have only been seen in patients with FVII deficiency. There have been no confirmed reports of antibodies against factor VII in hemophilia A or hemophilia B patients.
Nervous system disorders	
Very rare (<1/10,000)	- Headache - Paresthesia
Skin and subcutaneous tissue disorders	
Very rare (<1/10,000)	- Skin rashes including rash, maculopapular rash, urticara and pruritus

Post-Market Adverse Drug Reactions	
Vascular disorders	
Very rare (<1/10,000)	- Venous thrombotic events including portal vein thrombosis, pulmonary embolism, deep vein thrombosis, sub clavian vein thrombosis, jugular vein thrombosis, superior vena caval occlusion, renal vein thrombosis, thrombophlebitis and venous thrombosis limb - Arterial thromboembolic events including myocardial infarction and ischemia, cerebral infarction, cerebral ischemia, cerebrovascular disorders, ischemic stroke, thrombotic stroke, transient ischemic attack, renal artery thrombosis and intestinal ischemia - Mixed thromboembolic events including intracardiac thrombosis and thrombosis - Flushing Incidents of hemorrhage have been reported. **NiaStase**® is not expected to precipitate hemorrhage, but pre-existing hemorrhage may continue in case of insufficient efficacy or sub-optimal dosage regimen.

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**® (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**® and coagulation factor concentrates is unknown.

Anti-fibrinolytics have been reported to reduce blood loss in association with surgery in hemophilia patients, especially in orthopaedic surgery and surgery in regions rich in fibrinolytic

activity, such as the oral cavity. Experience with concomitant administration of anti-fibrinolytics and **NiaStase**® treatment is, however, limited.

Drug-Drug Interactions

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 Creatine 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.
- Hemostasis evaluation should be used to determine the effectiveness of **NiaStase**® (eptacog alfa, activated) and to provide a basis for modification of the **NiaStase**® treatment schedule.
- **NiaStase**® should be given as early as possible after the start of a bleeding episode. Following the initial dose of **NiaStase**® further injections may be repeated. The duration of treatment and the interval between injections will vary with the severity of the haemorrhage, the invasive procedures or surgery being performed.
- In hereditary severe FVII-deficient patients, replacement therapy with **NiaStase**® 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**®.

Recommended Dose and Dosage Adjustment

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

NiaStase® Dosage

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.

Reconstitution:

Reconstitution should be performed using the following procedures.

- Always use aseptic technique.
- Bring **NiaStase**® (white, lyophilized powder) and the specified volume of diluent (Sterile Water for Injection, USP - without preservative) to room temperature, but not above 37°C (98.6°F).
- The specified volume of diluent corresponding to the amount of **NiaStase**® is as follows:

Parenteral Products:

Vial Size (mg)	Volume of Diluent to be Added to Vial (mL) *	Concentration of rFVIIa After Reconstitution (mg per mL)
1.2	2.2	0.6
2.4	4.3	0.6
4.8	8.5	0.6

* Commercially available Sterile Water for Injection, without preservatives.

- Remove caps from **NiaStase**® vial and diluent vial to expose the central portion of the rubber stoppers. Cleanse the rubber stoppers with an alcohol swab and allow to dry prior to use.
- Draw back the plunger of a sterile syringe (attached to a sterile needle) and admit air into the syringe.
- Inject the air into the vial containing Sterile Water for Injection (diluent).
- Withdraw the diluent and inject it into the **NiaStase**® vial through the centre of the rubber stopper (the **NiaStase**® vial does not contain vacuum).
- Gently swirl the **NiaStase**® vial until all the material is dissolved. The reconstituted solution is colourless. Do not shake the vial, as this will cause 'foaming'.

After reconstitution with the appropriate volume of diluent each vial contains 30 KIU/mL (0.6 mg/mL).

Administration

Administration should take place immediately or at least within 3 hours after reconstitution. Any unused solution should be discarded. Do not store reconstituted **NiaStase**® in syringes. **NiaStase**® 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. Administration should be performed using the following procedures.

- Always use an aseptic technique.
- Draw back the plunger of the sterile syringe (attached to the sterile transfer needle) and admit air into the syringe.
- Insert the needle into the vial of reconstituted **NiaStase**®. Inject the air into the vial and then withdraw the reconstituted material into the syringe.
- Remove and discard the transfer needle from the syringe; attach a suitable intravenous injection needle and administer.

OVERDOSAGE

Dose limiting toxicities of **NiaStase**® (eptacog alfa, activated) 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 **NiaStase**® and FVII, has been associated with overdose in patients with factor VII deficiency.

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® (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**® 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**® 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

Single-dose pharmacokinetic studies of **NiaStase**® (17.5, 35, and 70 µg/kg) exhibited linear kinetics. FVII clotting activities were measured in plasma drawn prior to and during a 24-hour period after **NiaStase**® administration.

NiaStase® is distributed into a volume corresponding to 2 to 3 times the plasma volume. The median apparent volumes of distribution at steady state and at elimination were 106 and 122 mL/kg in non-bleeding hemophiliacs and 103 and 121 mL/kg in bleeding hemophiliacs, respectively. Median clearance was 31 mL/kg/h in hemophiliacs who were not bleeding and 33 mL/kg/h in hemophiliacs during bleeding episodes. The elimination of **NiaStase**® was described by mean residence time and half-life (t½). In non-bleeding hemophiliacs, the median mean residence time was 3.4 hours and the median t½ was 2.9 hours. Compared with these results, elimination appeared faster in bleeding episodes, where the median mean residence time was 3 hours, and the median t½ was 2.3 hours. The median, *in vivo* plasma recovery was 46% in non-bleeding episodes and 43% in bleeding episodes.

STORAGE AND STABILITY

Temperature:

Store under refrigeration (2° to 8°C).
Do not freeze.
Do not store reconstituted **NiaStase**® (eptacog alfa, activated) in syringes.

Light:

Store in original package in order to protect from light.

Other:

The vials should not be used after the expiration date. **NiaStase**® should not be mixed with infusion solutions or given in a drip.

SPECIAL HANDLING INSTRUCTIONS

Each vial of reconstituted **NiaStase**® (eptacog alfa, activated) should be used within 3 hours.

Table 5 – Recommended Storage Period and Conditions for NiaStase®

Dosage Strength	Shelf-Life/Storage	After Reconstitution/Storage*
1.2 mg/vial	36 months/ 2-8°C, protect from light	24 hours/ 25°C or 2-8°C
2.4 mg/vial	36 months/ 2-8°C, protect from light	24 hours/ 25°C or 2-8°C
4.8 mg/vial	36 months/ 2-8°C, protect from light	24 hours/ 25°C or 2-8°C

* Chemical and physical stability has been demonstrated after reconstitution for 24 hours at 25°C. From a microbiological perspective, each vial of reconstituted NiaStase® should be used within 3 hours.

DOSAGE FORMS, COMPOSITION AND PACKAGING

NiaStase® (eptacog alfa, activated) is supplied as a white, lyophilized powder in single-use vials. There is one vial per package. The amount in milligrams and kilo-international units is stated on the label as follows:

- 1.2 mg per vial (60 KIU/vial)
- 2.4 mg per vial (120 KIU/vial)
- 4.8 mg per vial (240 KIU/vial)

The following non-medicinal ingredients are found in **NiaStase**®:

- sodium chloride (3 mg/mL)
- calcium chloride dihydrate (1.5 mg/mL)
- glycylglycine (1.3 mg/mL)
- polysorbate 80 (0.1 mg/mL)
- mannitol (30 mg/mL)

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®** (eptacog alfa, activated) is structurally similar to human plasma-derived Factor VIIa.

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

CLINICAL TRIALS

Five adequate and well-controlled studies (see Table 6) and several supporting studies have provided substantial evidence for the efficacy of **NiaStase**® (eptacog alfa, activated). In these trials hemophilia patients with inhibitors were treated with **NiaStase**® for several types of bleeding episodes and for hemostasis during surgical procedures. The efficacy rates of **NiaStase**® are shown in Table 8.

These efficacy results are consistent with results obtained in supporting clinical studies (see Table 7) with **NiaStase**®.

Using the FVIIa assay, the pharmacokinetic properties of **NiaStase**®were studied in 12 paediatric and 5 adult patients. 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 per kg body weight). Mean clearance was approximately 50% higher in paediatric patients relative to adults (78 versus 53 mL kg^{-1} h^{-1}), 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^{-1} in paediatric patients versus 159 mL kg^{-1} in adults.

Study demographics and trial design

Table 6 – Hemophilia A/B Patients with Inhibitors in Adequate and Well-Controlled Clinical Studies

Study #	Trial design	Dosage, route of administration and duration	Number 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/ USA 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

Study #	Trial design	Dosage, route of administration and duration	Number of Patients	No. Of Bleeding Episodes	Efficacy Endpoint
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 7 – 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/NA C/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 8 – Efficacy rates with NiaStase®

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 **NiaStase**® 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 **NiaStase**® 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 NiaStase®.*	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

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 **NiaStase®** (eptacog alfa, activated) alone, 50 U/kg of an activated prothrombin complex concentrate (aPCC) alone, or a combination of **NiaStase®** 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 **NiaStase®** administration. Administration of 50 U/kg aPCC and then 78 µg/kg **NiaStase®** 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 **NiaStase®** in combination with tranexamic acid demonstrated no interaction effect on coagulation parameters.

TOXICOLOGY

Carcinogenesis and Mutagenesis

The clastogenic activity of **NiaStase®** (eptacog alfa, activated) 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 **NiaStase®**. Gene mutation studies (e.g. Ames test) have not been performed with **NiaStase®**.

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 9 – 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®
(eptacog alfa, activated)

This leaflet is Part III of a three-part 'Product Monograph' published when **NiaStase®** was approved for sale in Canada and designed specifically for Consumers. This leaflet is a summary and will not tell you everything about **NiaStase®**. 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® or eptacog alfa (activated) is more commonly known as activated recombinant human blood coagulation Factor VII (rFVIIa). **NiaStase®** is a clotting factor produced using recombinant DNA technology. **NiaStase®** or rFVIIa is free of all human plasma components, eliminating any possibility of contamination through the blood. **NiaStase®** 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).

What it does:

NiaStase® 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®** with any other clotting products. However, your doctor may prescribe other therapies to be used at the same time as **NiaStase®**.

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 important nonmedicinal ingredients are:

calcium chloride dihydrate, glycylglycine, mannitol, polysorbate 80, sodium chloride**.**

What dosage forms it comes in:

NiaStase® as a freeze-dried powder is available in 1.2 mg (60 KIU), 2.4 mg (120 KIU) and 4.8 mg (240 KIU) vials. The freeze-dried powder in a vial is reconstituted (dissolved) with Sterile Water for Injection, USP.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- The extent of the risk of developing blood clots after using **NiaStase®** 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**®.

BEFORE you use **NiaStase**® talk to your doctor 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.

INTERACTIONS WITH THIS MEDICATION

Interactions with other drugs have not been established. Before using **NiaStase**®, talk to your doctor about any medicine you use.

PROPER USE OF THIS MEDICATION

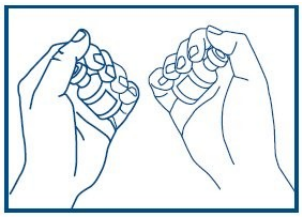
NiaStase® is available in three different strengths. Always check that you have the strength prescribed by your doctor. Always use an aseptic technique when injecting **NiaStase**®. For example follow the instructions for '*Preparing your injection' and 'Giving your injection'*. Bring the **NiaStase**® powder and the correct volume of diluent (Sterile Water for Injection, USP - without preservative) to room temperature but not above 37°C (98.6°F). You can do this by holding the vials in your hands for a few minutes.

The correct volume of diluent (Sterile Water for Injection, USP - without preservative) corresponding to each strength of **NiaStase**® is as follows:

- 1.2 mg (60 KIU) per vial add 2.2 mL Sterile Water for Injection, USP
- 2.4 mg (120 KIU) per vial add 4.3 mL Sterile Water for Injection, USP
- 4.8 mg (240 KIU) per vial add 8.5 mL Sterile Water for Injection, USP

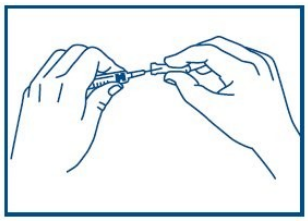
Preparing your injection

1. Wash your hands with soap and water before beginning.

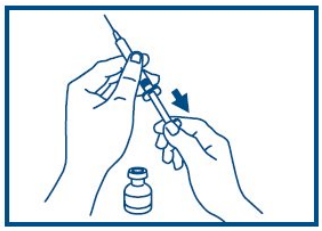


2. Hold vials to bring contents to room temperature.

3. Remove the caps, clean stoppers with an alcohol swab, and allow to dry prior to use.

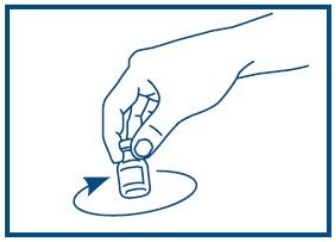


4. Attach needle to a sterile syringe and remove needle cap.

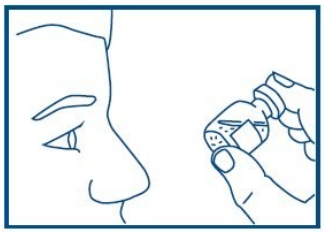


5. Admit air into the syringe and inject it into the vial containing the Sterile Water for Injection.

6. Withdraw the water and inject it into the vial containing the powder.



7. Gently swirl the vial until contents dissolve into a colourless solution. Do not shake the vial as this will cause foaming.



8. Inspect the vial solution for particles or discolouration. If the mixture is discoloured or contains particles, do not use it. Call your Hemophilia Care Centre or doctor.

Giving your injection

9. Inject **NiaStase**® as instructed by your Hemophilia Care Centre or doctor. Do not store reconstituted **NiaStase**® in syringes. Use the reconstituted product within 3 hours.

10. Discard unused solution and needles in a proper container.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

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 the drug and call your doctor
		Only if severe	In all cases	
Common	Redness at the injection site	✓		
Un common	Hives		✓	
	Itching		✓	
	Tightness of the 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®**, *contact your doctor.*

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.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:
Toll- free telephone: 1-866-234-2345
Toll-free fax: 1-866-678-6789
By e-mail: cadrmp@hc-sc.gc.ca
By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa, ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or Hemophilia Care Centre.

HOW TO STORE IT

Keep **NiaStase®** refrigerated, do not allow it to freeze.

Store in original package in order to protect from light.

Use each vial of reconstituted **NiaStase®** within 3 hours of mixing.

Do not use **NiaStase®** after the expiration date printed on the outer carton and on the vial label.

Do not store reconstituted **NiaStase®** in syringes.

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

MORE INFORMATION

For further information, please refer to the leaflet *'Health Professional Information'*.

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

This document plus the full product monograph, prepared for health professionals, is available by contacting the sponsor, **Novo Nordisk Canada Inc.**, at 1-800-465-4334

This leaflet was prepared by **Novo Nordisk Canada Inc.**

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