

# PRODUCT MONOGRAPH

Schedule D

**NiaStase RT<sup>®</sup>**  
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)

Professed

Coagulation Factor

**Novo Nordisk Canada Inc.**  
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**NiaStase RT<sup>®</sup>**  
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Activated Recombinant Human Blood Coagulation Factor VII Room Temperature Stable

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients</b>
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)	calcium chloride dihydrate, glycylglycine, mannitol, methionine, polysorbate 80, sodium chloride, sucrose.  The solvent for reconstitution of <b>NiaStase RT<sup>®</sup></b> contains histidine in water for injections.
<i>For a complete listing of nonmedicinal ingredients see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>		

**DESCRIPTION**

**NiaStase RT<sup>®</sup>** (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<sup>®</sup>** (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.

## 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**<sup>®</sup> (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).
- Patients with inherent Factor VII deficiency may have pre-existing or may develop anti-Factor VII antibodies during therapy with **NiaStase RT**<sup>®</sup>. 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 the risk of thromboembolic complications, caution should be exercised when administering **NiaStase RT**<sup>®</sup> (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**<sup>®</sup> 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 **rFVIIa** including myocardial infarction, myocardial ischemia, cerebral infarction and cerebral ischemia.

Patients who receive **NiaStase RT**<sup>®</sup> 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<sup>®</sup>** dosage should be reduced or treatment stopped, depending on the patient's symptoms.

Patients self-administering **NiaStase RT<sup>®</sup>** 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<sup>®</sup>** 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<sup>®</sup>** 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 RT<sup>®</sup>**, 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.

### **Carcinogenesis and Mutagenesis**

No chronic carcinogenicity studies have been performed with **NiaStase RT<sup>®</sup>**. 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<sup>®</sup>** 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<sup>®</sup>** should be made taking into account the benefit of breast-feeding to the child and the benefit of **NiaStase RT<sup>®</sup>** 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).

### **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 **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<sup>®</sup>** in patients.

Monitoring the effectiveness of therapy, the need for additional doses of **NiaStase RT<sup>®</sup>** 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.

<b>Criteria for Administration of Additional Treatment</b>	
Subjects with persistent moderate or severe pain following <b>rFVIIa</b> treatment	Subjects with persistent mild pain following <b>rFVIIa</b> 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<sup>®</sup>** therapy. Severity of bleeding condition and clinical response to **NiaStase RT<sup>®</sup>** 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 hemophilia and inhibitors is considered to be low.

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

Patients who receive **NiaStase RT<sup>®</sup>** (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 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 **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  $\geq 1\%$  of rFVIIa Treatment Episodes and were considered to be possibly related to rFVIIa administration.**

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

<b>Parameter</b>	<b>Shift*</b>	<b>No. Of Treatment Episodes Experiencing Shift (%)</b>	<b>Total No. of Treatment Episodes Evaluated</b>
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**

<b>Parameter</b>	<b>Shift*</b>	<b>No. Of Treatment Episodes Experiencing Shift (%)</b>	<b>Total No. of Treatment Episodes Evaluated</b>
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 Reaction Overview in Clinical Trials using NiaStase RT<sup>®</sup>**

The safety profile of **NiaStase RT<sup>®</sup>** 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<sup>®</sup>** 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<sup>®</sup>** (24 subjects) and/or **NiaStase<sup>®</sup>** (24 subjects) in the NN1007-1744 trial. A total of 24 patients with hemophilia were exposed to a single dose of **NiaStase RT<sup>®</sup>** 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<sup>®</sup>** and **NiaStase<sup>®</sup>** (see CLINICAL TRIALS, Comparative Bioavailability Studies).

## **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**

<b>Post-Market Adverse Drug Reactions</b>	
<b><i>Blood and lymphatic disorders</i></b>	
Very rare (<1/10,000)	- Disseminated intravascular coagulation - Coagulopathy
<b><i>Gastrointestinal disorders</i></b>	
Very rare (<1/10,000)	- Nausea - Vomiting
<b><i>General disorders and administration site conditions</i></b>	
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 <b>NiaStase RT<sup>®</sup></b> is compliant with the recommended dosage as stated. See DOSAGE AND ADMINISTRATION.
<b><i>Immune system disorders</i></b>	
Very rare (<1/10,000)	- Immune mediated reactions including anaphylactic reaction, and hypersensitivity
<b><i>Investigations</i></b>	
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.
<b><i>Nervous system disorders</i></b>	
Very rare (<1/10,000)	- Headache - Paresthesia
<b><i>Skin and subcutaneous tissue disorders</i></b>	
Very rare (<1/10,000)	- Skin rashes including rash, maculopapular rash, urticaria and pruritus
<b><i>Vascular disorders</i></b>	
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

<b>Post-Market Adverse Drug Reactions</b>	
	<p>thrombosis</p> <p>- Flushing</p> <p>Incidents of hemorrhage have been reported. <b>NiaStase RT<sup>®</sup></b> is not expected to precipitate hemorrhage, but pre-existing hemorrhage may continue in case of insufficient efficacy or sub-optimal dosage regimen.</p>

### **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**

<b>Serious Drug Interactions</b>
<ul style="list-style-type: none"> <li>• <b>NiaStase RT<sup>®</sup></b> (eptacog alfa, activated) should not be mixed with infusion solutions or be given in a drip.</li> <li>• Simultaneous use of prothrombin complex concentrates, activated or not, should be avoided.</li> </ul>

#### **Overview**

The risk of a potential interaction between **NiaStase RT<sup>®</sup>** 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 **rFVIIa** 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 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.
- Hemostasis evaluation should be used to determine the effectiveness of **NiaStase RT<sup>®</sup>** (eptacog alfa, activated) and to provide a basis for modification of the **NiaStase RT<sup>®</sup>** treatment schedule.
- **NiaStase RT<sup>®</sup>** should be given as early as possible after the start of a bleeding episode. Following the initial dose of **NiaStase RT<sup>®</sup>** 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<sup>®</sup>** 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<sup>®</sup>**.

### **Recommended Dose and Dosage Adjustment**

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

## NiaStase RT<sup>®</sup> Dosage

Indication	Recommended Dose	Frequency and Duration
Bleeding episodes	90 µg/kg*	<ul style="list-style-type: none"> <li>• An initial dose of 90 µg/kg is recommended.</li> <li>• Dose may vary depending on bleed severity (see dose range).</li> <li>• Administer every 2 hours until clinical improvement is observed.</li> <li>• 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.</li> </ul>
Surgery	90 µg/kg	<ul style="list-style-type: none"> <li>• An initial dose of 90 µg/kg is recommended.</li> <li>• Dose may vary depending on surgery type (see dose range).</li> <li>• Administer prior to surgery and at least every 2 hours during the procedure.</li> <li>• 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.</li> <li>• Dosing may be repeated once during the 2-hour interval after surgery depending on the clinical status of the patient.</li> <li>• 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.</li> </ul>

\* 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***

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

The specified volume of histidine solvent corresponding to the amount of **NiaStase RT<sup>®</sup>** is as follows:

<b>NiaStase RT<sup>®</sup> Vial Size (mg)</b>	<b>Volume of Histidine Solvent to be Added to Vial (mL)</b>	<b>Approximate Concentration of rFVIIa After Reconstitution (mg per mL)</b>
1.0	1.1	1.0
2.0	2.1	1.0
5.0	5.2	1.0

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

### **Administration**

Administration should take place immediately. If not used immediately after reconstitution, the vial may be stored at room temperature (below 30°C) or refrigerated for up to 3 hours. Any unused solution should be discarded. Do not freeze reconstituted **NiaStase RT<sup>®</sup>** or store in syringes.

**NiaStase RT<sup>®</sup>** 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 discoloration prior to administration, whenever the solution and container permit. Do not use if particulate matter or discoloration is observed.

For detailed instructions on how to administer **NiaStase RT<sup>®</sup>** 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 overdoses 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.

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**<sup>®</sup> (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**<sup>®</sup> 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**<sup>®</sup> 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/kg.h, and the mean terminal half-life ranged from 3.9 to 6.0 hours.

### Hemophilia A and B with Inhibitors

Using the FVIIa assay, the pharmacokinetic properties of **rFVIIa** were studied in 12 pediatric 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 pediatric patients relative to adults (78 versus 53 mL kg<sup>-1</sup> h<sup>-1</sup>), 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<sup>-1</sup> in pediatric patients versus 159 mL kg<sup>-1</sup> in adults.

## **STORAGE AND STABILITY**

Prior to reconstitution, keep **NiaStase RT**<sup>®</sup> powder and the histidine solvent refrigerated or store between 2° to 30°C. Do not freeze. Protect powder and solvent from light. Do not use past the expiration date.

After reconstitution, **NiaStase RT**<sup>®</sup> may be stored either at room temperature (below 30°C) or refrigerated for up to 3 hours. Do not freeze reconstituted **NiaStase RT**<sup>®</sup> or store it in syringes.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

**NiaStase RT<sup>®</sup>** (eptacog alfa, activated) is supplied as a white, lyophilized powder in single-use vials. There is one vial per package. The vials are 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.

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)

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

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

### Histidine Solvent

The solvent for reconstitution of **NiaStase RT<sup>®</sup>** is a 10 mmol solution of histidine in water for injection and is supplied as a clear colourless solution. The vials are 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.

## 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  $\gamma$ -carboxylated in the Glu-residues (partial  $\gamma$ -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<sup>®</sup>** (eptacog alfa, activated) is structurally similar to human plasma-derived Factor VIIa.

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

## **CLINICAL TRIALS**

No clinical studies were undertaken with **NiaStase RT<sup>®</sup>**, to establish the safety and efficacy of **NiaStase RT<sup>®</sup>** in the approved indications. The only exception is a single dose bioequivalence pharmacokinetic study (NN1007-1744) in healthy male subjects (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 – 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/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/D OS-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	<b>Prior to surgery</b> 90 µg/kg bolus dose for both groups, followed by:  <b>The bolus injection group</b> During procedure and Days 1- 5: 90 µg/kg every 2 hours; Days 6-10: 90 µg/kg every 4 hours  <b>The continuous infusion group</b> Days 1-5: 50 µg/kg/h; Days 6 - 10: 25 µg/kg/h	36	36 (major surgeries)	Investigator evaluation of hemostasis.

**Table 6 – 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/N AC	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**

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 % <i>100% efficacy rate demonstrated in the 90 µg/kg dose group</i>	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.  <i>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.</i>	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.  <i>Comparing i.v. bolus and i.v. continuous infusion of rFVIIa.</i>	75% for both treatment groups. <i>Based on the Global Hemostasis Treatment Evaluation for overall success in achieving and maintaining hemostasis at the end of the study period.</i>	HAEM-2011

## Comparative Bioavailability Studies

Trial NN1007-1744 was a single-centre, randomised, double-blind, two-way cross-over trial investigating the bioequivalence of **NiaStase**<sup>®</sup> (the marketed formulation of rFVIIa) and **NiaStase RT**<sup>®</sup> (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**<sup>®</sup> and **NiaStase RT**<sup>®</sup>. Secondary objectives were to compare the rFVIIa pharmacokinetic parameters and to investigate the short term safety and tolerability of **NiaStase RT**<sup>®</sup> 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**<sup>®</sup>/**NiaStase**<sup>®</sup>) 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 8).

**Table 8 - Mean Values and 90% Confidence Interval for the Ratio of NiaStase RT<sup>®</sup>/**NiaStase**<sup>®</sup> of Pharmacokinetic Parameters**

<b>NiaStase RT<sup>®</sup> (90 µg/kg) From measured data<sup>a</sup></b>				
<b>Parameter</b>	<b>NiaStase RT<sup>®</sup> (Test)</b>	<b>NiaStase<sup>®</sup> (Reference)</b>	<b>% Ratio of Geometric Means</b>	<b>90% Confidence Interval</b>
AUC <sub>T</sub> <sup>b</sup> , h*IU/mL	112.36	120.18	93.5	[ 90.0 ; 97.1 ]
AUC <sub>I</sub> <sup>b</sup> , h*IU/mL	112.37	120.19	93.5	[ 90.0 ; 97.1 ]
C <sub>MAX</sub> <sup>b</sup> , IU/mL	52.77	54.86	96.2	[ 93.1 ; 99.3 ]
T <sub>MAX</sub> <sup>c,d</sup> , hours	0.08 (NA.)	0.08 (NA.)		
T <sub>½</sub> <sup>c</sup> , 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 <sub>Max</sub> 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 9 – Long Term Toxicity Studies in Animals**

<b>Animal Species</b>			
<b>Rat</b>	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 <b>rFVIIa</b> were present. There was a dose-dependant increase in clotting activity.	
<b>Dog</b>	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 <b>rFVIIa</b> were present.	
<b>Monkey</b>	At 15 mg/kg/day toxicity was observed; this led to the female being sacrificed. Antibodies against <b>rFVIIa</b> 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 <b>rFVIIa</b> . 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).

**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, glycyglycine, 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) and 5.0 mg (250 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**

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<sup>®</sup> 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 RT<sup>®</sup>.

For instructions on how to prepare and administer NiaStase RT<sup>®</sup> please refer to the sections ‘Preparing Your Injection’ and ‘Giving Your Injection’ located at the end of this insert.

## 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<sup>®</sup>.

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	
<b>Common</b>	Redness at injection site	✓		
<b>Uncommon</b>	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<sup>®</sup>, contact your doctor.*

## 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: [cadmp@hc-sc.gc.ca](mailto:cadmp@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

Prior to reconstitution, keep **NiaStase RT**<sup>®</sup> powder and histidine solvent refrigerated or store between 2° to 30°C. Do not freeze. Protect powder and solvent from light. Do not use past the expiration date on the label.

After reconstitution, **NiaStase RT**<sup>®</sup> should be used immediately. If you do not use immediately after mixing, **NiaStase RT**<sup>®</sup> may be stored either at room temperature (below 30°C) or refrigerated for up to 3 hours. Do not freeze or store reconstituted **NiaStase RT**<sup>®</sup> 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:


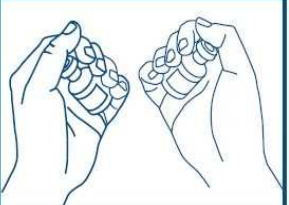

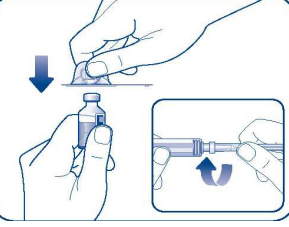
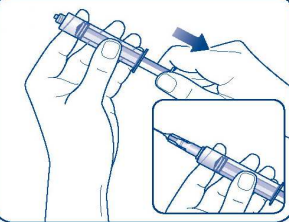
<http://www.novonordisk.ca> or by contacting Novo Nordisk Canada Inc., at: 1-800-465-4334

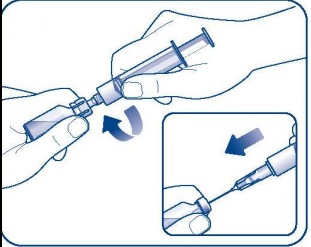
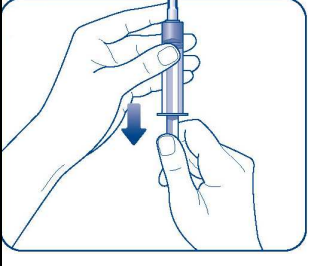
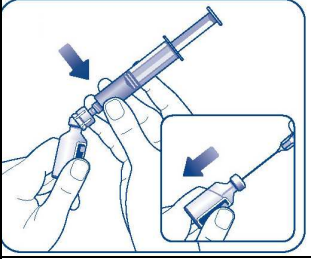
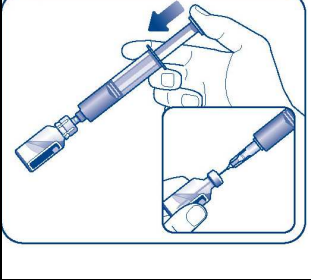
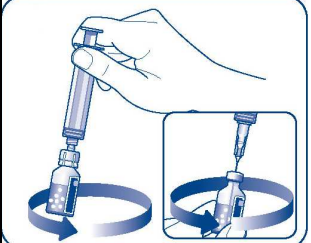
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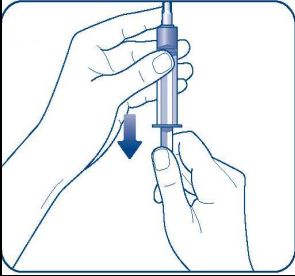
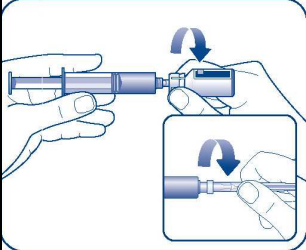


Last revised: March 2010

## PREPARING YOUR INJECTION

<p><b>Step 1</b></p>		<p>Wash your hands with soap and water before beginning and dry with a clean towel.</p>
<p><b>Step 2</b></p>		<p><b>NiaStase RT<sup>®</sup></b> powder and histidine solvent vials should be at room temperature at reconstitution. If not at room temperature, hold vials to bring contents to room temperature.</p>
<p><b>Step 3</b></p>		<p>Remove the plastic caps from the two vials. If the caps are loose or missing, do not use the vials. Clean the rubber stoppers on the vials with alcohol swabs, and allow them to dry prior to use.</p> <p>When preparing your injection, you can either use a vial adapter or a needle. Instructions on using the vial adapter and needle are provided below.</p>
<p><b>Step 4</b></p>		<p>If using a vial adapter, remove the protective paper from the vial adapter without taking it out of the protective cap. Attach the vial adapter to the histidine solvent vial. Once attached, remove the protective cap. Take care not to touch the spike on the vial adapter.</p> <p>If using a needle, remove the needle from the packaging without taking off the protective cap. Screw the transfer needle tightly onto the syringe. It is recommended to use syringe needles of gauge size 20-26.</p>
<p><b>Step 5</b></p>		<p>Pull the plunger to draw in a volume of air that is equal to the amount of histidine solvent in the solvent vial (mL equals cc on the syringe).</p>

<p><b>Step 6</b></p>		<p>Screw the syringe tightly onto the vial adapter on the histidine solvent vial.</p> <p>If using a needle, remove the protective cap and insert the needle into the rubber stopper of the histidine solvent vial. Take care not to touch the end of the transfer needle.</p> <p>Inject the air into the vial by pushing the plunger until you feel a clear resistance.</p>
<p><b>Step 7</b></p>		<p>Hold the syringe with the histidine solvent vial upside down. If you are using a transfer needle, make sure that the needle tip is in the solvent. Pull the plunger to draw the correct amount of histidine solvent into the syringe. The correct volume of histidine solvent corresponds to the strength of <b>NiaStase RT</b><sup>®</sup> that you have been given.</p> <ul style="list-style-type: none"> <li>• Withdraw 1.1 mL of solvent, if using a 1.0 mg vial of <b>NiaStase RT</b><sup>®</sup></li> <li>• Withdraw 2.1 mL of solvent, if using a 2.0 mg vial of <b>NiaStase RT</b><sup>®</sup></li> <li>• Withdraw 5.2 mL of solvent, if using a 5.0 mg vial of <b>NiaStase RT</b><sup>®</sup></li> </ul>
<p><b>Step 8</b></p>		<p>Once the histidine solvent has been drawn, remove the empty solvent vial.</p> <p>If you use a vial adapter, tip the syringe to remove it from the vial.</p>
<p><b>Step 9</b></p>		<p>Attach the syringe with vial adapter or transfer needle to the powder vial.</p> <p>If you use a transfer needle, insert the needle through the centre of the rubber stopper of the vial containing the powder. Aim the needle against the side of the vial so that the stream of the histidine solvent runs down the vial wall.</p> <p>Push the plunger slowly to inject the histidine solvent into the powder vial. Make sure not to aim the stream of solvent directly at the <b>NiaStase RT</b><sup>®</sup> powder, as this will cause foaming.</p>
<p><b>Step 10</b></p>		<p>Keep the vial adapter or transfer needle attached to the vial. Gently swirl the vial until all the powder is dissolved into a colourless solution. Do not shake the vial as this will cause foaming. Inspect the vial solution for visible particles or discolouration. If the mixture is discoloured or contains particles, do not use it. The reconstituted product should be used immediately. If you do not use immediately after reconstitution, <b>NiaStase RT</b><sup>®</sup> may be stored either at room temperature (below 30°C) or refrigerated for up to 3 hours.</p>

## GIVING YOUR INJECTION

<p><b>Step 11</b></p>		<p>Ensure that the plunger is pushed all the way in before turning the syringe upside down (it may have been pushed out by the pressure in the syringe).</p> <p>If you are using a transfer needle, make sure that the transfer needle tip is in the solution.</p> <p>Hold the syringe with the vial upside down and pull the plunger to draw all the solution into the syringe.</p>
<p><b>Step 12</b></p>		<p>If you are using a vial adapter, unscrew the vial adapter from the empty vial.</p> <p>If you are using a transfer needle, remove the transfer needle from the vial and cover the needle with the needle cap. Twist the transfer needle off the syringe.</p>
<p><b>Step 13</b></p>		<p>Attach a suitable intravenous injection device to the syringe and inject <b>NiaStase RT</b><sup>®</sup> as instructed by your Hemophilia Care Centre or doctor. Do not store reconstituted <b>NiaStase RT</b><sup>®</sup> in syringes.</p>
<p><b>Step 14</b></p>		<p>Safely dispose of the syringe, vials, needles, any unused product and other waste materials as instructed by your healthcare professional.</p>