NovoSeven® RT

1 mg, 2 mg, 5 mg and 8 mg
powder and solvent for solution for injection

Qualitative and quantitative composition
eptacog alfa (activated) 1 mg/vial (corresponds to 50 KIU/vial), 1 mg/ml after reconstitution
eptacog alfa (activated) 2 mg/vial (corresponds to 100 KIU/vial), 1 mg/ml after reconstitution
eptacog alfa (activated) 5 mg/vial (corresponds to 250 KIU/vial), 1 mg/ml after reconstitution
eptacog alfa (activated) 8 mg/vial (corresponds to 400 KIU/vial), 1 mg/ml after reconstitution

1 KIU equals 1,000 IU (International Units)
eptacog alfa (activated) is recombinant coagulation factor VIIa (rFVIIa) with a molecular mass of approximately 50,000 Daltons produced in baby hamster kidney cells (BHK Cells) by recombinant DNA technology.

Excipients
After reconstitution 1 ml solution contains 10 mg sucrose.
For a full list of excipients, see *List of excipients*.

Pharmaceutical form
Powder and solvent for solution for injection.
White lyophilised powder. Solvent: clear colourless solution. The reconstituted solution has a pH of approximately 6.0.

Clinical particulars
Therapeutic indications
NovoSeven® RT is indicated for the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures in the following patient groups:
- in patients with congenital haemophilia with inhibitors to coagulation factors VIII or IX > 5 BU
- in patients with congenital haemophilia who are expected to have a high anamnestic response to factor VIII or factor IX administration
- in patients with acquired haemophilia
- in patients with congenital FVII deficiency
- in patients with Glanzmann's thrombasthenia with antibodies to GP IIb - IIIa and/or HLA, and with past or present refractoriness to platelet transfusions.

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8-9022-00-024-1

Posology and method of administration
Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders.

Dosage
Haemophilia A or B with inhibitors or expected to have a high anamnestic response
Dose
NovoSeven® RT should be given as early as possible after the start of a bleeding episode. The recommended initial dose, administered by intravenous bolus injection, is 90 µg per kg body weight.
Following the initial dose of NovoSeven® RT 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.

Dosing in children
Current clinical experience does not warrant a general differentiation in dosing between children and adults, although young children have faster clearance than adults. Therefore, higher doses of rFVIIa may be needed in paediatric patients to achieve similar plasma concentrations as in adult patients, see *Pharmacokinetic properties*.

Dose interval
Initially 2–3 hours to obtain haemostasis.
If continued therapy is needed, the dose interval can be increased successively once effective haemostasis is achieved to every 4, 6, 8 or 12 hours for as long as treatment is judged as being indicated.

Mild to moderate bleeding episodes (including home therapy)
Early intervention has been shown to be efficacious in the treatment of mild to moderate joint, muscle and mucocutaneous bleeds. Two dosing regimens can be recommended:
1) Two to three injections of 90 µg per kg body weight administered at three-hour intervals. If further treatment is required, one additional dose of 90 µg per kg body weight can be administered.
2) One single injection of 270 µg per kg body weight.

The duration of the home therapy should not exceed 24 hours.
There is no clinical experience with administration of a single dose of 270 µg per kg body weight in elderly patients.

Serious bleeding episodes
An initial dose of 90 µg per kg body weight is recommended and could be administered on the way to the hospital where the patient is usually treated. The following dose varies according to the type and severity of the haemorrhage. Dosing frequency should initially be every second hour until clinical improvement is observed. If continued therapy is indicated, the dose interval can then be increased to 3 hours for 1–2 days. Thereafter, the dose interval can be increased successively to every 4, 6, 8 or 12 hours for as long as treatment is judged as being indicated. A major bleeding episode may be treated for 2–3 weeks but can be extended beyond this if clinically warranted.

Invasive procedure/surgery
An initial dose of 90 µg per kg body weight should be given immediately before the intervention. The dose should be repeated after 2 hours and then at 2–3 hour intervals for the first 24–48 hours depending on the intervention performed and the clinical status of the patient. In major surgery, the dose should be continued at 2–4 hour intervals for 6–7 days. The dose interval may then be increased to 6–8 hours for another 2 weeks of treatment. Patients undergoing major surgery may be treated for up to 2–3 weeks until healing has occurred.

Acquired haemophilia
Dose and dose interval
NovoSeven® RT should be given as early as possible after the start of a bleeding episode. The recommended initial dose, administered by intravenous bolus injection, is 90 µg per kg body weight. Following the initial dose of NovoSeven® RT further injections may be given if required. The duration of treatment and the interval between injections will vary with the severity of the haemorrhage, the invasive procedures or the surgery being performed.
The initial dose interval should be 2–3 hours. Once haemostasis has been achieved, the dose interval can be increased successively to every 4, 6, 8 or 12 hours for as long as treatment is judged to be indicated.

Factor VII deficiency
Dose, dose range and dose interval
The recommended dose range for treatment of bleeding episodes and for the prevention of bleeding in patients undergoing surgery or invasive procedures is 15–30 µg per kg body weight every 4–6 hours until haemostasis is achieved. Dose and frequency of injections should be adapted to each individual.

Glanzmann's thrombasthenia
Dose, dose range and dose interval
The recommended dose for treatment of bleeding episodes and for the prevention of bleeding in patients undergoing surgery or invasive procedures is 90 µg (range 80–120 µg) per kg body weight at intervals of two hours (1.5–2.5 hours). At least three doses should be administered to secure effective haemostasis. The recommended route of administration is bolus injection as lack of efficacy may appear in connection with continuous infusion. For those patients who are not refractory, platelets are the first line treatment for Glanzmann's thrombasthenia.

Method of administration
Reconstitute the solution as described in NovoSeven® RT user instructions and slowly administer as an intravenous bolus injection over 2–5 minutes.

Monitoring of treatment – laboratory tests
There is no requirement for monitoring of NovoSeven® RT therapy. Severity of bleeding condition and clinical response to NovoSeven® RT administration must guide dosing requirements. After administration of rFVIIa, prothrombin time (PT) and activated partial thromboplastin time (aPTT) have been shown to shorten, however no correlation has been demonstrated between PT and aPTT and clinical efficacy of rFVIIa.

Contraindications
Hypersensitivity to the active substance, the excipients, or to mouse, hamster or bovine protein.

Special warnings and precautions for use
In pathological conditions in which tissue factor may be expressed more extensively than considered normal, there may be a potential risk of development of thrombotic events or induction of Disseminated Intravascular Coagulation (DIC) in association with NovoSeven® RT treatment. Such situations may include patients with advanced atherosclerotic disease, crush injury, septicaemia or DIC. Because of the risk of thromboembolic complications, caution should be exercised when administering NovoSeven® RT to patients with a history of coronary heart disease, to patients with liver disease, to patients undergoing major surgery, 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 NovoSeven® RT should be weighed against the risk of these complications.
As recombinant coagulation factor VIIa 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 antihistamines i.v. should be considered.
If allergic or anaphylactic-type reactions occur, the administration should be discontinued immediately. In case of anaphylactic shock, standard medical treatment for shock should be implemented. Patients should be informed of the early signs of hypersensitivity reactions. If such symptoms occur, the patient should be advised to discontinue use of the product immediately and contact their physician.
In case of severe bleeds, the product should be administered in hospitals preferably specialised in treatment of haemophilia patients with coagulation factor VIII or IX inhibitors, or if not possible, in close collaboration with a physician specialised in haemophilia treatment.
If bleeding is not kept under control, hospital care is mandatory. Patients/carers should inform the physician/supervising hospital at the earliest possible opportunity about all usages of NovoSeven® RT.
Factor VII deficient patients should be monitored for prothrombin time and factor VII coagulant activity before and after administration of NovoSeven® RT. In case the factor VIIa activity fails to reach the expected level or bleeding is not controlled after treatment with the recommended doses, antibody formation may be suspected and analysis for antibodies should be performed.
Thrombosis has been reported in FVII deficient patients receiving NovoSeven® RT during surgery but the risk of thrombosis in factor VII deficient patients treated with NovoSeven® RT is unknown, see *Pharmacodynamic properties*.
Patients with rare hereditary problems of fructose intolerance, glucose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

Interaction with other medicinal products and other forms of interaction
The risk of a potential interaction between NovoSeven® RT and coagulation factor concentrates is unknown. Simultaneous use of prothrombin complex concentrates, activated or not, should be avoided.
Anti-fibrinolytics have been reported to reduce blood loss in association with surgery in haemophilia 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.
Based on a non-clinical study (see *Preclinical safety data*) it is not recommended to combine rFVIIa and rFXIII.
There are no clinical data available on interaction between rFVIIa and rFXIII.

Pregnancy and lactation
Pregnancy
As a precautionary measure it is preferable to avoid the use of NovoSeven® RT during pregnancy. Data on a limited number of exposed pregnancies within approved indications indicate no adverse effects of rFVIIa on pregnancy or on the health of the foetus/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/foetal development, parturition or postnatal development, see *Preclinical safety data*.

Lactation
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 NovoSeven® RT should be made taking into account the benefit of breast-feeding to the child and the benefit of NovoSeven® RT therapy to the woman.

Effects on ability to drive and use machines
No studies on the effect on the ability to drive and use machines have been performed.

Undesirable effects
The frequencies of both serious and non-serious adverse drug reactions are listed by system organ classes below.

Blood and lymphatic system disorders
Rare (> 1/10,000, < 1/1,000)
– Disseminated intravascular coagulation and related laboratory findings including elevated levels of D-dimer and decreased levels of AT, see *Special warnings and precautions for use*
– Coagulopathy

Immune system disorders
Rare (> 1/10,000, < 1/1,000)
– Hypersensitivity (see *Contraindications* and *Special warnings and precautions for use*)

Not known
– Anaphylactic reaction

Nervous system disorders
Rare (> 1/10,000, < 1/1,000)
– Headache

Vascular disorders
Rare (> 1/10,000, < 1/1,000)
– Arterial thromboembolic events: (myocardial infarction, cerebral infarction, cerebral ischaemia, cerebral artery occlusion, cerebrovascular accident, renal artery thrombosis, peripheral ischaemia, peripheral arterial thrombosis and intestinal ischaemia)
– Angina pectoris

Uncommon (> 1/1,000, < 1/100)
– Venous thromboembolic events: (deep vein thrombosis, thrombosis at i.v. site, pulmonary embolism, thromboembolic events of the liver including portal vein thrombosis, renal vein thrombosis, thrombophlebitis, superficial thrombophlebitis and intestinal ischaemia)

Not known
– Intracardiac thrombus

Gastrointestinal disorders
Rare (> 1/10,000, < 1/1,000)
– Nausea

Skin and subcutaneous disorders
Uncommon (> 1/1,000, < 1/100)
– Rash (including allergic dermatitis and rash erythematous)
– Pruritus and urticaria

Not known
– Flushing
– Angioedema

General disorders and administration site conditions
Uncommon (> 1/1,000, < 1/100)
– Therapeutic response decreased*
– Pyrexia

Rare (> 1/10,000, < 1/1,000)
– Injection site reaction including injection site pain

Investigations
Rare (> 1/10,000, < 1/1,000)
– Increased fibrin degradation products
– Increase of alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase and prothrombin.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Adverse drug reaction reported post-marketing only (i.e. not in clinical trials) are presented with a frequency of not known.

*Lack of efficacy (therapeutic response decreased) has been reported. It is important that the dosage regimen of NovoSeven® RT is compliant with the recommended dosage as stated in *Dosage*. Thromboembolic events may lead to cardiac arrest.

Patients with acquired haemophilia
Clinical trials conducted in 61 patients with acquired haemophilia with a total of 100 treatment episodes, showed that certain adverse drug reactions were reported more frequent (1% based on treatment episodes): Arterial thromboembolic events (cerebral artery occlusion, cerebrovascular accident), venous thromboembolic events (pulmonary embolism and deep vein thrombosis), angina pectoris, nausea, pyrexia, erythematous rash and investigation of increased levels of fibrin degradation products.

Inhibitory antibody formation
In post-marketing and clinical experience, there have been no confirmed reports of inhibitory antibodies against NovoSeven® RT or FVII in patients with haemophilia A or B. Development of inhibitory antibodies to NovoSeven® RT has been reported in a post-marketing observational registry of patients with congenital FVII deficiency.
In clinical trials of patients with factor VII deficiency, formation of antibodies against NovoSeven® RT and FVII is the only adverse drug reaction reported (frequency: common (≥ 1/100 to < 1/10)). In some cases, the antibodies showed inhibitory effect *in vitro*. Risk factors that may have contributed to antibody development including previous treatment with human plasma and/or plasma-derived factor VII, severe mutation of FVII gene and overdose of NovoSeven® RT, were present. Patients with factor VII deficiency treated with NovoSeven® RT should be monitored for factor VII antibodies (see *Special warnings and precautions for use*).

Thromboembolic events
When NovoSeven® RT is administered to patients outside approved indications, arterial thromboembolic events are common (≥ 1/100 to < 1/10). A higher risk of arterial thromboembolic adverse events (see *Undesirable effects; Vascular disorders*) (5.3% in patients treated with NovoSeven® RT versus 2.8% in placebo-treated patients) has been shown in a meta-analysis of pooled data from placebo-controlled trials conducted outside current approved indications in various clinical settings, each of these having distinct patient characteristics and hence different underlying risk profiles.
Safety and efficacy of NovoSeven® RT have not been established outside the approved indications and therefore NovoSeven® RT is not recommended.

Overdose
Dose limiting toxicities of NovoSeven® RT have not been investigated in clinical trials.
A few cases of overdose have been reported in patients with haemophilia. The only complication reported in connection with an overdose was a slight transient increase in blood pressure in a 16 year-old patient receiving 24 mg rFVIIa instead of 5.5 mg.
No cases of overdose have been reported in patients with acquired haemophilia or Glanzmann's thrombasthenia.
In patients with factor VII deficiency, where the recommended dose is 15–30 µg/kg rFVIIa, one episode of overdose has been associated with a thrombotic event (occipital stroke) in an elderly (> 80 years) male patient treated with 10–20 times the recommended dose. In addition, the development of antibodies against NovoSeven® RT and FVII has been associated with overdose in one patient with factor VII deficiency.
The dose schedule should not be intentionally increased above the recommended doses due to the absence of information on the additional risk that may be incurred.

Pharmacological properties
Pharmacodynamic properties
Pharmacotherapeutic group: Blood Coagulation factors, ATC code: B02BD08
NovoSeven® RT contains activated recombinant coagulation factor VII. The mechanism of action includes the binding of factor VIIa to exposed tissue factor. This complex activates factor IX into factor IXa and factor X into factor Xa, leading to the initial conversion of small amounts of prothrombin into thrombin. Thrombin leads to the activation of platelets and factors V and VIII at the site of injury and to the formation of the haemostatic plug by converting fibrinogen into fibrin. Pharmacological doses of NovoSeven® RT activate factor X directly on the surface of activated platelets, localised 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.
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.
In an observational registry (F7HAEM-3578) covering subjects with congenital FVII deficiency 3 out of 91 surgical patients experienced thromboembolic events.

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

Haemophilia A and B with inhibitors
Using the FVIIa assay, the pharmacokinetic properties of NovoSeven® RT were studied in 12 paediatric (2–12 years) and five adult patients in non-bleeding state. Dose proportionality was established in children for the investigated doses of 90 and 180 µg per kg body weight, which is in accordance with previous findings at lower doses (17.5–70 µg/kg rFVIIa). The mean clearance was approximately 50% higher in paediatric patients relative to adults (78 versus 53 ml/h×kg), whereas the mean terminal half-life was determined to 2.3 hours in both groups. Mean volume of distribution at steady state was 196 ml/kg in paediatric patients versus 159 ml/kg in adults. Clearance appears related with age, therefore in younger patients clearance may be increased by more than 50%.

Factor VII deficiency
Single dose pharmacokinetics of rFVIIa, 15 and 30 µg per kg body weight, showed no significant difference between the two doses used with regard to dose-independent parameters: total body clearance (70.8–79.1 ml/h×kg), volume of distribution at steady state (280–290 ml/kg), mean residence time (3.75–3.80 h), and half-life (2.82–3.11 h). The mean *in vivo* plasma recovery was approximately 20%.

Glanzmann's thrombasthenia
The pharmacokinetics of NovoSeven® RT in patients with Glanzmann's thrombasthenia have not been investigated, but are expected to be similar to the pharmacokinetics in haemophilia A and B patients.

Preclinical safety data
All findings in the preclinical safety programme were related to the pharmacological effect of rFVIIa. A potential synergistic effect of combined treatment with rFXIII and rFVIIa in an advanced cardiovascular model in cynomolgus monkey resulted in exaggerated pharmacology (thrombosis and death) at a lower dose level than when administering the individual compounds.

Pharmaceutical particulars
List of excipients
Powder
Sodium chloride, calcium chloride dihydrate, glycylglycine, polysorbate 80, mannitol, sucrose, methionine, hydrochloric acid (for pH-adjustment) and sodium hydroxide (for pH-adjustment).

Solvent
Histidine, hydrochloric acid (for pH-adjustment), sodium hydroxide (for pH-adjustment) and water for injections.

Incompatibilities
NovoSeven® RT must not be mixed with infusion solutions or be given in a drip.

Shelf life
After reconstitution, chemical and physical stability has been demonstrated for 6 hours at 25°C and 24 hours at 5°C.
From a microbiological point of view, the product should be used immediately. If not used immediately, storage time and storage conditions prior to use are the responsibility of the user, and should not be longer than 24 hours at 2°C–8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Special precautions for storage
– Store powder and solvent below 25°C
– Store powder and solvent protected from light
– Do not freeze to prevent damage to the solvent vial
– For storage conditions of the reconstituted medicinal product, see *Shelf life*.

Nature and contents of container
Each NovoSeven® RT package contains:
– 1 vial with white powder for solution for injection
– 1 vial with solvent for reconstitution.

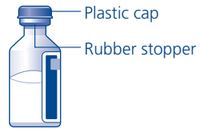
The NovoSeven® RT package contains:
Type I glass vials closed with a chlorobutyl rubber stopper, covered with an aluminium cap.
The closed vials are equipped with a tamper-evident snap-off cap which is made of polypropylene.
Not all pack sizes may be marketed.

Marketing authorisation holder
Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd, Denmark

NOVOSEVEN® RT USER INSTRUCTIONS

Solvent vial

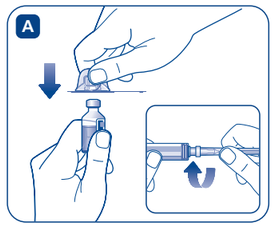
Powder vial



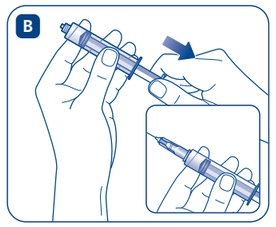
Preparing the solution

Wash your hands. NovoSeven® RT powder and solvent vials should be at room temperature at reconstitution. 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 before use. Use a disposable syringe of an appropriate size and a vial adapter, transfer needle (20–26G) or other suitable device.

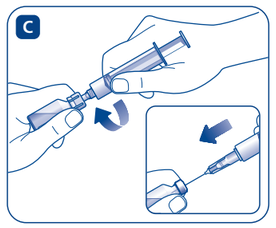
A Remove the protective paper from the vial adapter without taking it out of the protective cap. Attach the vial adapter to the solvent vial. Once attached, remove the protective cap. Take care not to touch the spike on the vial adapter. If using a needle, remove the needle from the packaging without taking it out of the protective cap. Screw the transfer needle tightly onto the syringe.



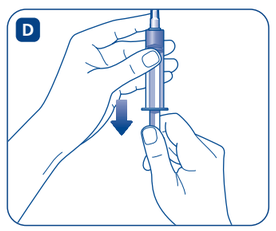
B Pull the plunger to draw in a volume of air that is equal to the amount of solvent in the solvent vial (ml equals cc on the syringe).



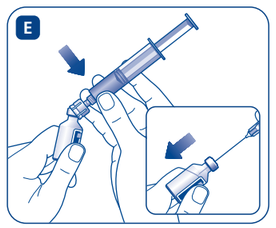
C Screw the syringe tightly onto the vial adapter on the solvent vial. If using a needle, remove the protective cap and insert the needle into the rubber stopper of the solvent vial. Take care not to touch the end of the transfer needle. Inject air into the vial by pushing the plunger until you feel a clear resistance.



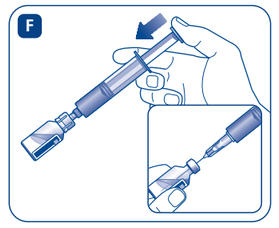
D Hold the syringe with the solvent vial upside down. If you are using a transfer needle, make sure that the needle tip is in the solvent. Pull the plunger to draw the solvent into the syringe.



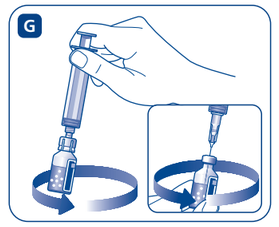
E Remove the empty solvent vial. If you use a vial adapter, tip the syringe to remove it from the vial.



F Attach the syringe with vial adapter or transfer needle to the powder vial. If you use a transfer needle, make sure to penetrate the centre of the rubber stopper. Hold the syringe slightly tilted with the vial facing downwards. Push the plunger slowly to inject the solvent into the powder vial. Make sure not to aim the stream of solvent directly at the NovoSeven® RT powder as this will cause foaming.



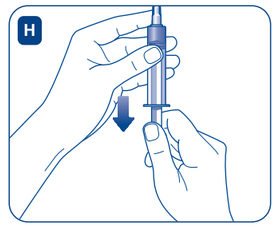
G Gently swirl the vial until all the powder is dissolved. Do not shake the vial as this will cause foaming. Check the solution for visible particles and discolouration. If you notice either, do not use it. NovoSeven® RT reconstituted product is a clear, colourless solution. Keep the vial adapter or transfer needle attached to the vial.



Although NovoSeven® RT will be stable for 24 hours after it has been mixed, you should use it at once to avoid infection. If you do not use it immediately after mixing, you should store the vial with the syringe still attached in a refrigerator at 2°C to 8°C for no longer than 24 hours. Do not store the solution without your doctor's advice.

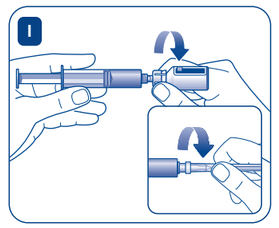
Injecting the solution

H 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). If you use a transfer needle, make sure that the transfer needle tip is in the solution. Hold the syringe with the vial upside down and pull the plunger to draw all the solution into the syringe.



I If you use a vial adapter, unscrew the vial adapter with the empty vial. If you use a transfer needle, remove the transfer needle from the vial, replace the needle cap, and twist the transfer needle off the syringe.

NovoSeven® RT is now ready for injection. Follow the injection procedure as instructed by your healthcare professional.



J Safely dispose of the syringe, vials, any unused product and other waste materials as instructed by your healthcare professional.