TO: National Bleeding Disorders Foundation
From: Novo Nordisk
SUBJECT: NovoSeven® RT (coagulation Factor VIIa, recombinant) and Novoeight® (antihemophilic factor, recombinant) U.S. Supply Disruptions

Dear NBDF Leadership,

As part of our commitment to sharing timely and transparent information, we want to provide you with an important update about NovoSeven® RT (coagulation Factor VIIa, recombinant).

We have identified an issue on a specific production line that is manufacturing NovoSeven® RT. This issue has resulted in the potential under-filling of some 1 mg and 2 mg NovoSeven® RT vials on the market. However, the likelihood of an under-filled vial reaching the market is very low (0.062% or 1 in 1,600 vials, equating to a probability of less than 10 vials in the U.S) due to extensive manual inspections during production, which resulted in most under-filled vials being identified and removed before release.

Although they are filled on the same line as NovoSeven® RT, there are no under-filled vials of Novoeight® (antihemophilic factor, recombinant) or Esperoct® [antihemophilic factor (recombinant), glycopegylated-exei].

It is important to note that Novo Nordisk's medical evaluation of NovoSeven® RT 1mg and 2 mg on the market concluded that under-filled vials can still be used in treatment and the probability of serious adverse health consequences is remote. **Please click here for NovoSeven® RT Prescribing Information, including Boxed Warning.**

This manufacturing issue has led to a temporary shortage of the NovoSeven® RT 1 mg and 2 mg vials and some strengths of Novoeight® at the Novo Nordisk Distribution Center (NNDC).

- NovoSeven® RT
    - The NovoSeven® RT 1 mg and 2 mg vials are both back in stock at the NNDC as of June 21, 2024 for the 2 mg vial, and as of June 27, 2024 for

the 1 mg vial. During the temporary stock-out, both vial sizes remained available at some Novo Nordisk Authorized Distributors.
    - The NovoSeven® RT 5 mg vials are fully available.
    - The 8 mg vial is back in stock as of June 24, 2024. Its availability was not related to the under-filling issue associated with the 1 mg and 2 mg vials.

- Novoeight®
    - Novoeight® 1000 IU and 2000 IU vial sizes are expected to be out of stock until the end of July 2024, and Novoeight® 500 IU and 3000 IU vial sizes are expected to be out of stock at the NNDC from mid-June until the end of July 2024. However, we expect stock of the 500 IU, 1000 IU, 2000 IU, and 3000 IU vials sizes to be available at authorized specialty distributors. We continue to have an adequate stock of Novoeight® 250 IU and 1500 IU vial sizes.

Based on our current understanding and inventory levels of NovoSeven® RT and Novoeight®, additional shortages are expected to be intermittent and to continue at least throughout 2024 due to this manufacturing issue, combined with unrelated release delays from the packaging line, and other continued capacity constraints. We will keep you informed if any occur.

We have informed the U.S. Food and Drug Administration (FDA) of the current situation and are proactively engaging in dialog with various stakeholders, including healthcare professionals, HTCs, specialty pharmacies as well as professional and patient advocacy groups, to provide updates on our supply situation.

[To help you address questions you may be receiving from patients, we have attached a template letter you can adapt to send to patients, if you deem it appropriate.]

We understand the impact this may have on patients, their families, and physicians. We are dedicated to continuing our support for the community and ensuring the availability of these therapies.

In the interim, if you have any questions, please reach out to your Novo Nordisk representative or contact Novo Care customer support at 1-844-668-6732. We've included

answers to the most frequently asked questions below should you need additional information.

Frequently Asked Questions

Q1: How and when did we learn about the under-filling issue?

A1: This issue, which is estimated to have affected NovoSeven® RT batches since October 2023, was detected through a Novo Nordisk internal quality process carried out during the first week in May leading to a halt in manufacturing on May 14, 2024.

Q2: When did we communicate to the FDA?

A2: Once we understood the production situation, we notified the FDA in accordance with regulatory requirements and timelines, on June 12.

Q3: Have any adverse events (including breakthrough bleeding) been reported to Novo Nordisk about the impacted batches of NovoSeven® RT 1 mg and 2 mg?

A3: No customer complaints or adverse events have been received about any of the affected packaging batches of NovoSeven® RT 1 mg and 2 mg produced by the affected filling line.

Q4: How many vials are affected by under-filling?

A4: Less than 0.062% of NovoSeven® RT 1mg and 2mg vials on the market are affected (which is less than 1 in every 1,600 vials). This means the likelihood of a patient receiving an under-filled vial is very low. Novo Nordisk's medical evaluation concluded that under-filled vials can still be used in treatment and the probability of serious adverse health consequences is remote.

Q5: What is the degree of under-filling in affected vials?

A5: The extensive manual inspection during manufacturing allowed for a 100% detection of vials that contained less than 50% of the target volume. For this reason, the under-filled vials that have reached the market are expected to have more than 50% of the intended content. As a consequence, the estimated frequency of under-filled vials of NovoSeven® RT 1mg and 2mg on the market is 0.062% (1 in 1,600) for vials filled 50-

80% compared to target, equating to a probability of less than 10 vials in the U.S. This means the likelihood of a patient receiving an under-filled vial is very low.

Q6: How many under-filled vials may have been identified?
A6: There are 10,477 1 mg vials and 5,300 2 mg vials for the U.S. market that have been in batches identified with this issue. The chance that any of these vials are under-filled is very low (0.062% or 1 in 1,600 vials), equating to a probability of less than 10 vials in the U.S.

Q7: Why have you decided not to recall?

A7: We have informed the U.S. Food and Drug Administration (FDA) of the current situation. Novo Nordisk's medical evaluation concluded that treatment with under-filled doses will still be effective, and the probability of serious adverse health consequences is remote. In addition, a recall would have caused immediate unavailability. This would have impacted the thousands of patients across the globe that depend on NovoSeven® RT, especially those in countries without other alternative therapy options.

Q8: Can we communicate the batch numbers externally?

A8: The vast majority of NovoSeven® RT 1 mg and 2 mg vials are unaffected. All currently available batches may have a vial that is under-filled at a rate of 0.062% or 1 in 1,600 vials, equating to a probability of less than 10 vials in the U.S. across all batches. In addition, it is not possible to identify a vial that is under-filled, and so we are advising that an HCP follow dosing guidance and to monitor clinical response as per label. **Please** click here **for NovoSeven® RT Prescribing Information, including Boxed Warning.**

Q9: Is the rationale that 'the clinical risk of treating with under-filled vials is less because 1 and 2 mg vials are usually pooled' valid for infants?

A9: Even in the infrequent situations where doses are low and could be managed with a single vial, such as with infants, redosing based on clinical response and monitoring of adequate hemostasis is emphasized in the label and clinical practice. Based on the low frequency by which underfill could occur, the risk of two consecutive vials being under filled is remote. **Please** click here **for NovoSeven® RT Prescribing Information, including Boxed Warning.**

Q10: I still have concerns about using an under-filled vial when dosing pediatric patients.

A10: Repeat dosing until hemostasis is achieved is recommended in the label for all patients including pediatrics and adults. In addition, Novo Nordisk's medical evaluation concluded that treatment with under-filled vials will still have an effect, and the probability of serious adverse health consequences is remote. For babies weighing 6 kg or less, even with a remote chance of receiving a vial less than 50% filled, it would make a therapeutic dose consistent with the label. For patients weighing between 6 kg and 22 kg, you could consider giving (2) 1 mg vials instead of (1) 2 mg vial because the chances of having 2 under-filled 1 mg vials is 1 in 2 million." **Please click here for NovoSeven® RT Prescribing Information, including Boxed Warning.**

Q11: What is the impact for a patient receiving under-filled NovoSeven® RT?

A11: Novo Nordisk's medical evaluation of NovoSeven® RT 1mg and 2 mg on the market concluded that under-filled vials can still be used in treatment and the probability of serious adverse health consequences is remote. The likelihood of a patient receiving an under-filled vial is very low (0.062% or 1 in 1,600 vials that are filled 50%-80% compared to target, equating to a probability of less than 10 vials in the U.S.), due to extensive manual inspections during production, which resulted in most under-filled vials being identified and removed before release.

1 mg and 2 mg vials are commonly used in combination with additional vials for treatment, and the likelihood of combining under-filled vials is extremely low, resulting in minimal likelihood of impact on therapeutic dose. As per the label, NovoSeven® RT treatment recommendations indicate dosing ranges for the treatment of bleeds, with repeated dosing until hemostasis is achieved.

Treatment of severe bleeding usually involves several injections. This means the impact of one under- filled 1 mg or 2 mg vial on the overall required treatment dose will likely be minimal. **Please** click here **for NovoSeven® RT Prescribing Information, including Boxed Warning.**

Q12: What is the guidance for patients with product on hand?

A12: The likelihood of an under-filled vial reaching the market is very low due to extensive manual inspections during production, which resulted in most under-filled vials being identified and removed before release. It is important to note that Novo

Nordisk's medical evaluation concluded that treatment with under-filled doses will still be effective and the probability of serious adverse health consequences is remote. Novo Nordisk is not recommending that patients discard NovoSeven® RT vials. If patients have concerns about the potential of having an under-filled vial, we encourage them to call their healthcare professional.

Q13: What is the timeline for communication with the community?
A13: Communication began on June 12, 2024. We have been notifying relevant health authorities in accordance with regulatory requirements, which means exact timelines will differ across countries.

Q14: When can we expect production to fully resume?

A14: The root cause of the issue has been identified, and production had been suspended on the specific line while we ran tests and validated processes. Production has fully resumed, but we do expect that this issue will lead to intermittent supply at least throughout 2024.

Q15: You have indicated that this is an issue with one production line. Where was this production line located? How long was the line functioning incorrectly before Novo identified the issue?
A15: The specific production line is a dedicated line for the filling of NovoSeven® RT, Novoeight®, and Esperoct® vials located in Denmark. The root cause was identified during the first week in May and is unique to this specific line. The issue is limited to batches filled at this specific vial filling line in Denmark from October 2023.

Q16: Why did it take so long to identify this issue?

A16: The combination of the very low number of vials being potentially under-filled and the low amount of underfill in those vials made detection difficult. Once we became aware of the issue, we stopped production. For the batches on market, the likelihood of an under-filled vial is very low. This is due to extensive manual inspections during production, as a result of which, most under-filled vials were identified and removed before release. This means the likelihood of a patient receiving an under-filled vial is very low (0.062% or 1 in 1,600 vials that are filled 50%-80% compared to target, equating to a probability of less than 10 vials in the U.S.).

Q17: How many total production lines are there for Novoseven® RT, Novoeight®, and Esperoct®?

A17: We have multiple lines producing Novoseven® RT, Novoeight®, and Esperoct®. Other production lines are running as per usual. The root cause has been identified and is unique to this specific line for vial filling.

Q18: Has Novo Nordisk verified that the other production lines are functioning correctly? How will Novo Nordisk ensure that they will continue to do so?

A18: Yes. Other production lines are running as per usual. Novo Nordisk follows strict GMP (Good Manufacturing Practices). All our sites are continuously monitored and inspected by global health authorities.

Q19: Why is it predominantly NovoSeven® RT and Novoeight® supply that is impacted?

A19: NovoSeven® RT and Novoeight® make up the biggest production volume. Therefore, the impact is more visible.

Q20: What other products are manufactured in this facility? Are they also at risk of this manufacturing issue?

A20: NovoSeven® RT, Novoeight®, and Esperoct® are manufactured on this specific production line. However, this specifically relates to potentially affected batches of NovoSeven® RT 1 mg and 2 mg. The likelihood of a patient receiving an under-filled vial is very low. Novoeight® and Esperoct® vials are not affected by this manufacturing issue.

Q21: Is under-filled NovoSeven® RT on the market? If so, where?

A21: 11 countries (Algeria, Brazil, Colombia, India, Kuwait, Lithuania, Malaysia, Mexico, Qatar, Saudi Arabia, and USA) have potentially affected batches of NovoSeven® RT 1 mg and 2 mg on the market. Health Authorities (HA) in the relevant countries are being informed, based on the local situation and requirements.

Q22: Is this manufacturing issue related to other drug shortages that Novo Nordisk is experiencing?

A22: No. It only concerns the specific production line at one of our manufacturing sites in Denmark and is not related to other drug-shortage situations.

Q23: Could under-filled Novoeight® or Esperoct® be on the market? If so, where?

A23: No. There are no under-filled batches of Novoeight® or Esperoct® on the market.

Q24: Which markets could face a shortage?

A24: This could potentially impact all markets where NovoSeven® RT and Novoeight® are approved. For NovoSeven® RT, only 1 mg and 2 mg vial sizes are affected. Based on our current understanding and inventory levels of NovoSeven® RT and Novoeight®, additional shortages are expected to be intermittent and to continue at least throughout 2024 due to this manufacturing issue, combined with unrelated release delays from the packaging line, and other continued capacity constraints. We will keep you informed if any occur.

We have informed the FDA of the current situation and are proactively engaging in dialogue with various stakeholders, including healthcare professionals, HTCs, specialty pharmacies as well as professional and patient advocacy groups, to provide updates on our supply situation. We understand the impact this may have on patients, their families, and physicians. We are dedicated to continuing our support for the community and ensuring the availability of these therapies.

Q25: Who should hospitals, HTCs, and SPs contact if they can't acquire NovoSeven® RT in the future?

A25: Hospitals, HTCs, and SPs should contact their specialty distributors regarding supply or potentially a secondary distributor during the period where stock of the 1 mg, 2 mg, and 8 mg vials are currently out at the NNDC. We encourage you to contact the Novo Nordisk ordering center to access a list of Authorized Distributors if your primary distributor does not have 1 mg or 2 mg vials on hand.

Q26: Are there safety concerns related to switching to alternative medicines in the instance of a stock out?

A26: All discussion of switching treatment should take place between the patient and their healthcare professional.

Q27: How long do you expect this shortage to last?

A27: All NovoSeven® RT strengths are back in stock, and we are taking all measures possible to ensure adequate supply. However, based on our current understanding and inventory levels of NovoSeven® RT and Novoeight®, additional shortages are expected to be intermittent and to continue at least throughout 2024 due to this manufacturing issue, combined with unrelated release delays from the packaging line, and other continued capacity constraints. We will keep you informed if any occur.

We have informed the FDA of the current situation and are proactively engaging in dialogue with various stakeholders including healthcare professionals, HTCs, specialty pharmacies as well as professional and patient advocacy groups, to provide updates on our supply situation. We understand the impact this may have on patients, their families, and physicians. We are dedicated to continuing our support for the community and ensuring the availability of these therapies.

Q28: How does this manufacturing/supply challenge affect Rebinyn® and Tretten®?

A28: This supply challenge does not affect Rebinyn® Coagulation Factor IX [(Recombinant)], GlycoPEGylated, or Tretten® Coagulation Factor XIII A-Subunit [(Recombinant)] as they are produced on different lines.

Q29: What do you mean when you say, "'intermittent supply' throughout 2024?"

A29: This means that the need to stop the production line to investigate the issue may cause further production delays that could cause additional stock out periods. We will keep you informed if we expect this to occur.

General

Q30: What is NovoSeven® RT and what is it indicated for?

A30: NovoSeven® RT (coagulation Factor VIIa, recombinant) is an injectable medicine used for:

- Treatment of bleeding and prevention of bleeding for surgeries and procedures in adults and children with hemophilia A or B with inhibitors, congenital Factor VII (FVII) deficiency, and Glanzmann's thrombasthenia with a decreased or absent response to platelet transfusions

- Treatment of bleeding and prevention of bleeding for surgeries and procedures in adults with acquired hemophilia

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Important Safety Information

What is the most important information I should know about NovoSeven® RT?

NovoSeven® RT may cause serious side effects, including:

- **Serious blood clots** that form in veins and arteries with the use of NovoSeven® RT have been reported
- Your healthcare provider should discuss the risks and explain the signs and symptoms of blood clots to you. Some signs of a blood clot may include pain, swelling, warmth, redness, or a lump in your legs or arms, chest pain, shortness of breath, or sudden severe headache and/or loss of consciousness or function
- Your healthcare provider should monitor you for blood clots during treatment with NovoSeven® RT
- You should not use NovoSeven® RT if you have ever had allergic (hypersensitivity) reactions, including severe, whole body reactions (anaphylaxis) to NovoSeven® RT, any of its ingredients, or mice, hamsters, or cows. Signs of allergic reaction include shortness of breath, rash, itching (pruritus), redness of the skin (erythema), or fainting/dizziness

What should I tell my healthcare provider before using NovoSeven® RT?

- Tell your healthcare provider if you have any of the following, as these may increase your risk of blood clots:
    - congenital hemophilia and are also receiving treatment with aPCCs (activated prothrombin complex concentrates)
    - are an older patient particularly with acquired hemophilia and receiving other agents to stop bleeding

    - history of heart or blood vessel diseases
- Tell your healthcare provider and pharmacist about all the medicines you take, including all prescription and non-prescription medicines, such as over-the-counter medicines, supplements, or herbal remedies

What are the possible side effects of NovoSeven® RT?

- The most common and serious side effects are blood clots
- Tell your healthcare provider about any side effects that bother you or do not go away, and seek medical help right away if you have signs of a blood clot or allergic reaction

Please click here for Prescribing Information, including Boxed Warning.

Sincerely,

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