Recombinant Treatments for Bleeding Disorders

An overview of treatments that are considered to have a low risk of viral transmission

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History of bleeding disorder treatments

Before recombinant products were developed, the management of bleeding disorders relied on products derived from human blood supply. Although these products provided a means of managing bleeding disorders, there remained a need to create a safer product. The timeline below shows a brief history of the treatment options.

1940s and earlier

Blood transfusions

- To replace missing clotting factors, blood infusions were given right after a spontaneous joint and muscle bleed

Late 1950s and early 1960s

Fresh Frozen Plasma, or FFP

- Plasma bags were transfused into patients in the hospital
- Because each plasma bag had a limited amount of clotting factor, huge volumes of FFP were required

1960s

Cryoprecipitate plasma

- After thawing plasma, the precipitate left over was found to be rich in factor VIII in a smaller volume
- Emergency surgery and elective procedures for patients with hemophilia became more routine

Late 1960s to 1970s

Factor concentrates

- Factor concentrates transformed hemophilia care because they could be stored at home
- This allowed patients to self-infuse factor products

Late 1970s to mid-1980s

HIV/AIDS and Hepatitis C infections

- ~5,000 patients with hemophilia were infected with HIV through contaminated factor products
- Thousands of patients with hemophilia died of AIDS*
- 44% of all people with hemophilia contracted Hepatitis C

*More than 4,000 patients died of AIDS by 2002. Most of the deaths were in the 1990s.

1990s Recombinant factor products

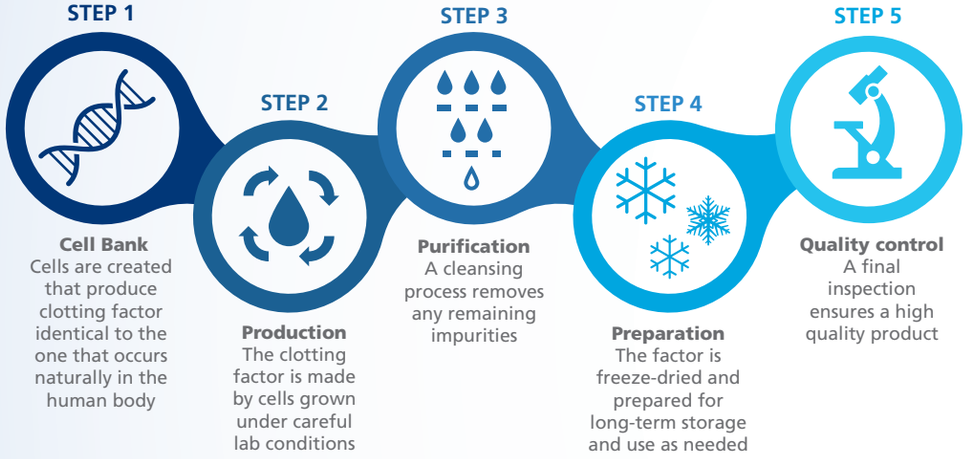
- First bleeding disorder treatment that was not made from human blood or plasma

Recombinant products: A significant advance

What does recombinant mean?

- The word recombinant means that the product is made in a laboratory
- Recombinant factor products are produced in cell lines engineered to include the gene for human clotting factors
- Although the cell lines are considered to be free of viruses, they undergo additional steps to ensure safety and purity

How are recombinant factor products made?



With recombinant products, there is a low risk of exposure to viruses that are derived from human blood or plasma.

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What do medical experts say about recombinant products?

- The National Hemophilia Foundation's Medical and Scientific Advisory Council, or MASAC, provides recommendations and advisories on treatment, research, and other general health concerns for the bleeding disorders community

Patient	MASAC Recommendation
Rare Bleeding Disorder	Recombinant Product if available
Previously Treated Patient with Hemophilia A or B	Recombinant Product
Previously Untreated Patient with Hemophilia A	Recombinant FVIII Product or Plasma-Derived FVIII Product Containing von Willebrand Factor

It is recommended that all patients, including those with hemophilia A or B that develop an inhibitor to factor VIII or IX, should consult with a health care professional to discuss the best treatment option.

Terms and Links

Glossary of Terms to Know

Bleed: A collection of blood in an area, such as muscle or joint.

Cell line: A cell culture grown from a single genetically altered cell to produce a recombinant protein.

Clotting: The process of forming into a clot or clots.

Clotting factors: Proteins in the blood that work together with platelets to form a fibrin clot in an injured blood vessel and stop bleeding. Clotting factors are named using Roman numerals (factor I [one] to factor XIII [thirteen]).

Factor: A protein in the blood that helps form blood clots.

FVIII/FIX: Two of the clotting factor proteins that help form blood clots.

Hemophilia: A bleeding disorder due to a factor deficiency. People with hemophilia A have a lack of factor VIII. People with hemophilia B have a lack of factor IX.

Hepatitis C: An infection caused by a virus that attacks the liver and leads to inflammation.

HIV: Human Immunodeficiency Virus. This virus damages the immune system and interferes with your body's ability to fight the organisms that cause disease.

Infuse: The act of injecting medicine directly into a vein using a needle and syringe.

Plasma: The liquid part of the blood that contains clotting factors and other proteins.

Precipitate: When a substance is deposited in solid form from a solution.

Recombinant: Genetically engineered DNA. Made in the lab.

Spontaneous: Something that happens on its own, for what seems like no reason. Spontaneous bleeding does not appear to be the result of a specific injury.

Resources

Canadian Hemophilia Society (CHS): **hemophilia.ca**

National Hemophilia Foundation (NHF): **hemophilia.org**

National Organization for Rare Disorders (NORD): **rarediseases.org**

World Federation of Hemophilia (WFH): **wfh.org**

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NovoSeven® RT
Coagulation Factor VIIa (Recombinant)

Indications and Usage

NovoSeven® RT (Coagulation Factor VIIa [Recombinant]) is 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 people with Glanzmann's thrombasthenia who have a decreased or absent response to platelet transfusions
- Treatment of bleeding and prevention of bleeding for surgeries and procedures in adults with acquired hemophilia

Important Safety Information

WARNING: BLOOD CLOTS

- 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.

Warnings and Precautions

- NovoSeven® RT should be used with caution if you have an increased risk for blood clots, such as with disseminated intravascular coagulation (DIC), clogged arteries, crush injury, septicemia (an infection in the blood), uncontrolled bleeding after giving birth, history of heart disease, liver disease, limited movement following surgery, in elderly people, in newborns, or if you are taking aPCCs/PCCs (activated or nonactivated prothrombin complex concentrates) with NovoSeven® RT.
- Allergic reactions, including serious whole body allergic reactions, have been reported with NovoSeven® RT. Tell your healthcare provider if you are allergic to NovoSeven® RT, any of its ingredients, or mice, hamsters, or cows. If you think you are having an allergic reaction, call your healthcare provider right away. Some signs of allergic reaction may include shortness of breath, rash, itching, redness of the skin, and fainting/dizziness.

Warnings and Precautions (cont'd)

- People with Factor VII deficiency should be monitored by their healthcare provider for antibodies, which can cause NovoSeven® RT to stop working properly.

Side Effects

- 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.

Use with Other Drugs

- Blood clots may occur if NovoSeven® RT is given with Coagulation Factor XIII (13).

Please see accompanying Prescribing Information in pocket.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

NovoSeven® RT is a prescription medication. Novo Nordisk provides patient assistance for those who qualify. Please call 1-877-NOVO-777 (1-877-668-6777) to learn more about Novo Nordisk assistance programs.

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novoeight®

Antihemophilic Factor (Recombinant)

Indications and Usage

Novoeight® (Antihemophilic Factor [Recombinant]) is an injectable medicine used to control and prevent bleeding in people with hemophilia A. Your healthcare provider may give you Novoeight® when you have surgery.

Novoeight® is not used to treat von Willebrand Disease.

Important Safety Information

You should not use Novoeight® if you are allergic to factor VIII or any of the other ingredients of Novoeight® or if you are allergic to hamster proteins.

Call your healthcare provider right away and stop treatment if you get any of the following signs of an allergic reaction: rashes or hives, difficulty breathing or swallowing, tightness of the chest, swelling of the lips and tongue, light-headedness, dizziness or loss of consciousness, pale and cold skin, fast heartbeat, or red or swollen face or hands.

Before taking Novoeight®, you should tell your healthcare provider if you have or have had any medical conditions, take any medicines (including non-prescription medicines and dietary supplements), are nursing, pregnant or planning to become pregnant, or have been told that you have inhibitors to factor VIII.

Your body can make antibodies called "inhibitors" against Novoeight®, which may stop Novoeight® from working properly. Call your healthcare provider right away if your bleeding does not stop after taking Novoeight®.

Important Safety Information (cont'd)

Common side effects of Novoeight® include swelling or itching at the location of injection, changes in liver tests, and fever.

Please see accompanying Prescribing Information in pocket.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Novoeight® is a prescription medication. Novo Nordisk provides patient assistance for those who qualify. Please call 1-877-NOVO-777 (1-877-668-6777) to learn more about Novo Nordisk assistance programs.

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tretten®

Coagulation Factor XIII A-Subunit (Recombinant)

Indications and Usage

What is Tretten® (Coagulation Factor XIII A-Subunit [Recombinant])?

- Tretten® is an injectable medicine used to prevent bleeding in adults and children who have congenital Factor XIII (FXIII) A-subunit deficiency.
- Tretten® is not for use in patients with congenital Factor XIII B-subunit deficiency.

Important Safety Information

Who should not use Tretten®?

- You should not use Tretten® if you have ever had allergic (hypersensitivity) reactions, including severe, whole body reaction (anaphylaxis) to Tretten® or any of the ingredients.

What should I tell my healthcare provider before Tretten® is given?

- Tell your healthcare provider about all of your medical conditions, including if you are pregnant, think you may be pregnant or planning to become pregnant, are breast feeding, or have a history of blood clots.
- Tell your healthcare provider and pharmacist about all of 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 Tretten®?

- Call your healthcare provider or go to the emergency department right away if you have any of the following symptoms after using Tretten®:
  - Signs of allergic reaction, including shortness of breath, rash, itching (pruritus), redness of the skin (erythema), or fainting/dizziness.
  - Signs of a blood clot including pain, swelling, warmth, redness, or a lump in your legs or arms, chest pain, or sudden severe headache and/or loss of consciousness or function.
  - Unexpected bleeding.

What are the possible side effects of Tretten®? (cont'd)

- Other possible side effects may include pain in your arms or legs, headache, and pain at the injection site.
- These are not all the possible side effects of Tretten®. Tell your healthcare provider about any side effect that bothers you or that does not go away.

Please see accompanying Prescribing Information in pocket.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Tretten® is a prescription medication. Novo Nordisk provides patient assistance for those who qualify. Please call 1-844-Tretten (1-844-873-8836) to learn more about Novo Nordisk assistance programs.

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The Novo Nordisk commitment to you

Novo Nordisk has multiple recombinant treatments available for you and the bleeding disorders community

NovoSeven® RT
Coagulation Factor VIIa (Recombinant)

novoeight®
Antihemophilic Factor (Recombinant)

tretten®
Coagulation Factor XIII A-Subunit (Recombinant)

Talk to your Novo Nordisk representative to learn more about Novo Nordisk recombinant treatment options

Indications and Usage for NovoSeven® RT

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Selected Important Safety Information

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- Your healthcare provider should monitor you for blood clots during treatment with NovoSeven® RT.

Please see additional Important Safety Information on pages 6 through 11.
Please see accompanying Prescribing Information in pocket.

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