

ABOUT HEMOPHILIA

What is hemophilia and how common is it?

The word hemophilia derives from two Greek words: haima, meaning blood, and philia, meaning affection. Hemophilia is a hereditary condition. This means that it is passed on from mother to child at the time of conception. The blood of a person with hemophilia does not clot normally. He does not bleed more profusely or more quickly than other people; however, he bleeds for a longer time.

Many people believe that hemophiliacs bleed a lot from minor cuts. This is a myth. External wounds are usually not serious. Far more important is internal bleeding (hemorrhaging). These hemorrhages are in joints, especially knees, ankles and elbows; and into tissues and muscles. When bleeding occurs in a vital organ, especially the brain, a hemophiliac's life is in danger.

Both hemophilia A and B are very rare disorders. Hemophilia A affects fewer than 1 in 10,000 people, or about 2,500 Canadians. Hemophilia B is even less common, affecting approximately 1 in 50,000 people, or about 600 Canadians.

Who is affected by hemophilia?

Hemophilia affects people of all races, colours and ethnic origins.

The most severe forms of hemophilia affect almost only males. Females can be seriously affected only if the father is a hemophiliac and the mother is a carrier, or in the case of X-inactivation when a woman's normal X-chromosome is inactive in the production of factor VIII or IX. These cases are extremely rare.

However, many women who are carriers have symptoms of mild hemophilia. We are only now fully recognizing the importance of bleeding in carriers and the degree to which these symptoms affect a woman's quality of life.

As hemophilia is a hereditary disorder, people are affected at birth. This means that children can have hemophilia. In fact, hemophilia is often diagnosed in the first year of life.

How serious is hemophilia?

Without proper treatment, hemophilia is crippling and often fatal. With modern treatment, most people with hemophilia can lead full, active lives.

Hemophilia is classified as severe, moderate or mild.

CLASSIFICATION	LEVEL OF FACTOR VIII OR IX IN THE BLOOD
Severe	Less than 1% of normal
Moderate	1 to 5% of normal
Mild	5 to 30% normal

Severe hemophiliacs with less than 1% of the normal level of factor VIII or IX in the blood have hemorrhages several times a month. The bleeding is often the result of a minor bump or twist. Sometimes, there is often no apparent cause for the bleeding.

Moderate hemophiliacs bleed less often. Their hemorrhages are often the result of minor trauma, such as a sports injury.

Mild hemophiliacs have even fewer hemorrhages. They may be aware of their bleeding problem only in the case of surgery, a tooth extraction or a serious injury. Women with mild hemophilia may bleed more during menstruation (periods).¹

The clotting problem in hemophilia

Blood is carried throughout the body within a network of blood vessels. When tissues are injured, damage to a blood vessel may result in leakage of blood through holes in the vessel wall. The vessels can break near the surface, as in a cut. Or they can break deep inside the body, making a bruise or an internal hemorrhage.

Platelets are small cells circulating in the blood. Each platelet is less than 1/10,000 of a centimetre in diameter. There are 150 to 400 billion platelets in a normal litre of blood. The platelets play an important role in stopping bleeding by clumping together and forming a plug, thereby beginning the repair of injured blood vessels. Clotting factors like factor VIII and IX are then needed to glue the plug in place thus forming a clot.

When a blood vessel is damaged, there are four stages in the normal formation of a clot. Stage 1: The blood vessels are damaged and the bleedings starts.

Stage 2: The blood vessels constrict to slow the flow of blood to the injured area.

Stage 3: Platelets stick to, and spread on, the walls of damaged blood vessels. This is called platelet adhesion. These spreading platelets release substances that activate other nearby platelets which clump at the site of injury to form a platelet plug. This is called platelet aggregation.

Stage 4: The surface of these activated platelets then provides a site for blood clotting to occur. Clotting proteins like factor VIII and IX circulating in the blood are activated on the surface of the platelets to form a mesh-like fibrin clot.

These proteins (factors I, II, V, VII, VIII, IX, X, XI, XII, XIII and von Willebrand factor) work like dominos, in a chain reaction. This is called the coagulation cascade.

What is the clotting problem in hemophilia?

When one of the proteins, for example, factor VIII, is absent, the dominos stop falling, and the chain reaction is broken. Clotting does not happen, or it happens much more slowly than normal. The platelets at the site of the injury do not mesh into place to form a permanent clot. The clot is 'soft' and easily

¹ Canadian Hemophilia Society. 2012. What is hemophilia. <http://www.hemophilia.ca/en/bleeding-disorders/hemophilia-a-and-b/what-is-hemophilia/>

displaced. Without treatment, bleeding will continue until the pressure outside the broken vessel is equal to the pressure inside. This can take days and sometimes weeks.²

What is comprehensive hemophilia care?

Comprehensive hemophilia care is: all of the medical services needed by a hemophiliac and his family for the treatment of hemophilia and related conditions. This care is provided at a comprehensive care clinic.

This is a place where a person with hemophilia or a bleeding disorder can receive all the care he / she needs at one time. It is called a comprehensive care clinic because it offers a complete range of services.

The following people work there:

The medical director is often a hematologist who specializes in the area of blood clotting. He / she prescribe the lab tests to find out the exact bleeding problem; prescribes the proper treatment to control and prevent bleeding and monitors the overall health of the hemophiliac.

The nurse coordinator is the front-line person in the clinic. He/she helps families deal with the day-to-day problems related to hemophilia; answers families' questions over the phone or at the clinic and provides out-patient care at the clinic. He/she teaches families how to do home therapy; organizes the delivery of blood products for home use; and coordinates appointments with other members of the comprehensive care team.

The physiotherapist checks the hemophiliac's joints and muscles to make sure joint movement is not lost and that muscles remain strong; helps the hemophiliac with exercises to regain lost joint function or to rebuild muscles; and helps the hemophiliac to find a sports and exercise program to keep him in top shape.

The social worker's role is to help parents, siblings, and people with hemophilia and other family members, including carriers, deal with the impact that hemophilia can have on their lives.

The dentist provides dental care and works closely with the hematologist to prevent bleeding during dental work.

The comprehensive care team will add other individuals as needed, such as an obstetrician / gynecologist (to help women with bleeding problems); a genetic counsellor (to give information to carriers); an orthopedic specialist (for joint problems and joint surgery); an HIV specialist (for treatment related to HIV infection); and a hepatologist or gastroenterologist (for treatment related to hepatitis C infection).

What is home care?

Home care is the infusion of factor concentrates at home. In Canada most severe hemophiliacs are treated at home. This has major advantages over treatment at the hemophilia clinic or at the emergency

² Canadian Hemophilia Society. 2012. The clotting problem in hemophilia. <http://www.hemophilia.ca/en/bleeding-disorders/hemophilia-a-and-b/the-clotting-problem-in-hemophilia/>

room. These are: quicker treatment when a bleed starts; a more normal life for the hemophiliac and other members of the family; a greater acceptance of treatment by the young child and the ability for people to take care of their own health.

The comprehensive care clinic team trains the family with a young hemophiliac how to recognize bleeds and then how to infuse the factor concentrate. Children often learn how to infuse themselves at the age of eight or ten. Then, the hemophiliac is able to treat himself at home, at school, at camp or on vacation. Hemophiliacs on home care go to the comprehensive care clinic once or twice a year for a complete check-up.³

What is factor replacement therapy?

The basic treatment to stop or prevent bleeding in people with hemophilia A and B is factor replacement therapy. This is the infusion (injection into the bloodstream) of factor VIII and IX concentrates to prevent or control bleeding. These concentrates come from two sources - human plasma (a component of blood) and a genetically engineered cell line made by DNA technology, called recombinant.

In both cases, the factor VIII or IX protein is nearly identical to the protein which is lacking in the blood of hemophiliacs. After an infusion of the concentrate, all the proteins needed for clotting are in place. A hemophiliac's blood becomes 'normal', at least for a few hours. This allows the time for a clot to form at the site of the damaged blood vessel. (See the clotting problem in hemophilia.) Unfortunately, the replacement of the missing clotting factors is not permanent. Half of the clotting factor activity which was infused is removed by the body every 12 to 24 hours. This means that within 2 or 3 days almost none is left. The hemophiliac's blood is again unable to clot normally.

What are the advantages of today's factor concentrates?

The clotting factors available in Canada today have many advantages over products available in the 1950s, 1960s, 1970s and 1980s. These are the advantages.

- They are very concentrated. This means that a small amount contains enough factor VIII or IX activity to control bleeding, even in major surgery. Thus, they are very effective.
- They are convenient. The concentrates can be stored in a home refrigerator for up to a year or kept at room temperature for 3 to twelve months.
- They are easy to mix. A small amount of sterile water, about 5 to 10 millilitres, is mixed with the powdered concentrate. A few seconds to one minute later the preparation is ready to be infused.
- They are quick to infuse. From beginning to end, the infusion takes no more than 15 to 20 minutes.
- They are very safe. None of the factor VIII or IX concentrates, whether plasma-derived or recombinant, used in Canada since 1988 has ever been known to transmit HIV or hepatitis.

How are factor VIII and IX concentrates made?

³ Canadian Hemophilia Society. 2012. Comprehensive Hemophilia Care. <http://www.hemophilia.ca/en/bleeding-disorders/hemophilia-a-and-b/the-treatment-of-hemophilia/comprehensive-hemophilia-care>

Factor VIII and IX concentrates can be divided into two categories - recombinant, genetically engineered factor VIII and IX; plasma-derived factor VIII and IX.

Recombinant, genetically engineered factor VIII and IX

RECOMBINANT FACTOR VIII COMPARISON CHART

Product	Cell line, molecule	Half-life	Viral inactivation	Vial size	Reconstitution device	Storage	Availability
Advate Manufactured and distributed by Shire	Produced in a Chinese hamster ovary (CHO) cell line. Full-length factor VIII molecule.	Mean half-life of 13 hours in adults	Solvent detergent: Polysorbate 80	250 500 1,000 1,500 2,000 3,000 IUs	BAXJECT II	2-8°C, room temperature up to 28°C for up to 6 months	Licensed by Health Canada for all ages. Available in Quebec. Being phased out in rest of Canada in 2016.

Comments

Product monograph: www.baxter.ca/en/downloads/product_information/ADVATE_PM_Dec2013_EN.pdf

Product	Cell line, molecule	Half-life	Viral inactivation	Vial size	Reconstitution device	Storage	Availability
Afstyla Antihemophilic Factor VIII (Recombinant), SingleChain manufactured and distributed by CSL Behring	Produced in a Chinese hamster ovary (CHO) cell line. B-domain-deleted factor VIII molecule. The single-chain design results in high binding affinity of Afstyla to von Willebrand factor.	Mean half-life of 14 hours in adults	Nanofiltration Solvent detergent: Polysorbate 80	250 IUs (2.5 mL) 500 IUs (2.5 mL) 1,000 IUs (2.5 mL) 1,500 IUs (5 mL) 2,000 IUs (5 mL) 3,000 IUs (5 mL)	Mix2Vial	2-8°C, room temperature up to 25°C for up to 3 months	Licensed by Health Canada for all adults and children to control and prevent bleeds, for prophylaxis and for surgery. Not distributed in Canada.

Comments

Product monograph: <http://labeling.cslbehring.ca/PM/CA/AFSTYLA/EN/AFSTYLA-Product-Monograph.pdf>

Product	Cell line, molecule	Half-life	Viral inactivation	Vial size	Reconstitution device	Storage	Availability
Nuwiq Manufactured and distributed by Octapharma	Produced in a human embryonic kidney (HEK) cell line. B-domain deleted FVIII molecule.	Mean half-life of 15 hours in adults	A series of chromatography purification steps, virus inactivation, further purification by chromatography, a second dedicated viral removal step by nanofiltration, and a final purification step by size exclusion chromatography	250 500 1,000 2,000 IUs	2.5 mL diluent	2 to 8°C for up to 18 months, room temperature up to 25°C for up to 1 month	Approved by Health Canada for the treatment and prophylaxis of bleeding in patients of all ages. Not currently distributed in Québec. Available in rest of Canada.

Comments

Health Canada Basis of Decision: www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2015_nuwiq_169551-eng.php

Product monograph: www.octapharma.ca/fileadmin/user_upload/octapharma.ca/Product_Monographs/PM00031489_Nuwiq_EN.PDF

Product	Cell line, molecule	Half-life	Viral inactivation	Vial size	Reconstitution device	Storage	Availability
Xyntha Manufactured and distributed by Pfizer	Produced in a Chinese hamster ovary (CHO) cell line. B-domain-deleted factor VIII molecule.	Mean half-life of 11-12 hours in adults	Nanofiltration Solvent detergent: Polysorbate 80	250 500 1,000 2,000 3,000 IUs	R2 Kit Xyntha Solofuse all-in-one reconstitution device	2-8°C, room temperature up to 25°C for up to 3 months	Licensed by Health Canada for all ages. Distributed in all provinces.

Comments

Product monograph: www.pfizer.ca/sites/g/files/g10017036/f/201505/XYNTHA_PM_E_177952_12Jan2015.pdf

Product	Cell line, molecule	Half-life	Viral inactivation	Vial size	Reconstitution device	Storage	Availability
Zonovate (NovoEight in the rest of the world) Manufactured and distributed by Novo Nordisk	Produced in a Chinese hamster ovary (CHO) cell line. B-domain truncated FVIII molecule.	Mean half-life of 11-12 hours in adults	Purification steps include chromatography using a FVIII specific monoclonal antibody (mAb) immune affinity column and sterile filtration	250 500 1,000 1,500 2,000 3,000 IUs	MixPro with 4 mL diluent	2-8°C for 24 months, room temperature up to 30°C for a single period of up to 6 months	Approved by Health Canada for the peri-operative management treatment and prophylaxis of bleeding in patients of all ages. Not currently distributed by CBS or Héma-Québec.

Comments

Health Canada Basis of Decision: www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2015_zonovate_170796-eng.php

Product monograph: www.novonordisk.ca/content/dam/Canada/AFFILIATE/www-novonordisk-ca/OurProducts/PDF/Zonovate_PM_English.pdf

RECOMBINANT FACTOR IX

Product	Cell line, molecule	Half-life, recovery	Viral inactivation	Vial size	Reconstitution device	Storage	Availability
Alprolix Manufactured and distributed by Biogen Idec	Produced in a human embryonic kidney (HEK) cell line. Covalently linked to the Fc domain of recombinant human immunoglobulin G1 to extend half-life.	Half-life is 2.5 times longer than Benefix, permitting once-a-week infusions. Recovery is similar to Benefix.	Multiple viral clearance steps including 15 nm virus-retaining nano-filtration	250 500 1,000 2,000 3,000 IUs	Diluent provided in prefilled syringe (5 mL of diluent)	2°C to 8°C or up to 30°C for a single 6-month period	Licensed by Health Canada in 2014 for children and adults 12 years and older. Distributed on a limited basis for specific needs (short half-life, venous access problems) in Quebec. Available for most patients in rest of Canada.

Comments

Health Canada Basis of Decision: www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2014_alprolix_163614-eng.php

Product monograph: www.biogen.ca/content/dam/corporate/en_CA/pdfs/products/ALPROLIX/Alprolix-Product-Monograph-19Nov2015_E.pdf

Product	Cell line, molecule	Half-life, recovery	Viral inactivation	Vial size	Reconstitution device	Storage	Availability
BeneFIX Manufactured and distributed by Pfizer	Produced in a Chinese hamster ovary (CHO) cell line	Mean half-life of 19 hours in adults. 28% lower in-vivo recovery than with plasma-derived FIX.	Solvent detergent: Polysorbate 80	250 500 1,000 1,500 2,000 3,000 IUs	Diluent provided in prefilled syringe (5 mL of diluent)	Room temperature or under refrigeration, at a temperature of 2°C to 30°C	Licensed by Health Canada in 1997, distributed in all provinces. Indicated for the control and prevention of bleeding and for routine prophylaxis and surgery in patients of all ages.

Comments

Product monograph: www.pfizer.ca/sites/g/files/g10017036/t/201410/BENEFIX_PM_E_153056_27Dec2012.pdf

Product	Cell line, molecule	Half-life, recovery	Viral inactivation	Vial size	Reconstitution device	Storage	Availability
Idelvion Manufactured and distributed by CSL Behring	Produced in a Chinese hamster ovary (CHO) cell line. Fused to recombinant human albumin to extend half-life.	Half-life is 5 to 6 times longer than Benefix, permitting once-a-week infusions or less frequently. Recovery is superior to Benefix.	Two dedicated, orthogonal virus reduction steps including nanofiltration	250 500 1,000 2,000 IUs	Mix2Vial (2.5 mL of diluent for 250, 500 and 1,000 IU vials; 5 mL diluent for 2,000 IU vial)	Between 2°C and 25°C	Licensed by Health Canada in 2016 for treatment of bleeding, prophylaxis and surgery for all ages. Not currently available in Canada.

Comments

Health Canada Basis of Decision: www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd-smd-2016-idelvion-180793-eng.php

Product monograph: <http://labeling.cslbehring.ca/PM/CA/IDELVION/EN/IDELVION-Product-Monograph.pdf>

Product	Cell line, molecule	Half-life, recovery	Viral inactivation	Vial size	Reconstitution device	Storage	Availability
Rixubis Manufactured and distributed by Shire	Produced in a Chinese hamster ovary (CHO) cell line	Standard half-life similar to Benefix Recovery similar to Benefix	Solvent detergent and 15 nm nanofiltration	250 500 1,000 2,000 3,000 IUs	BAXJECT II (5 mL of diluent)	2°C to 8°C for up to 24 months; Room temperature not to exceed 30°C for up to 12 months	Licensed by Health Canada in 2015 for adults to control bleeding and for prophylaxis and surgery. Not currently available in Canada.

Comments

Product monograph: www.baxalta.ca/downloads/Product_Monographs/en/Rixubis.pdf

Recombinant, genetically engineered factor VIII and IX are not made from human plasma. They are made like this:

- The human factor VIII (or IX) gene is isolated through genetic engineering. The gene contains the code which has instructions for the cell on how to make human factor VIII (or IX).
- The gene is inserted into non-human cells, such as baby hamster kidney cells or Chinese hamster ovary cells.
- These cells are grown in a cell culture. They produce factor VIII (or IX).
- The factor VIII (or IX) is separated from the cell culture and purified.
- Sucrose is then added to stabilize the final factor VIII (or IX) product.

Plasma-derived factor VIII and IX

Plasma-derived factor VIII and IX are made from human plasma. Plasma donations are pooled together in a pharmaceutical plant. Then, the plasma is separated into different products. This is called fractionation. The main products are:

- albumin (to treat burns)
- immune globulins (to treat problems of the immune system)
- factor VIII (to treat hemophilia A)
- factor IX (to treat hemophilia B).

The plasma-derived clotting factor concentrates available in Canada have an excellent safety record - no cases of transmitting HIV, hepatitis B or C. Plasma-derived blood products go through four separate safety steps.

- Each blood donor is questioned each time he / she gives blood to find out if he / she has a greater than normal risk of carrying a blood-borne virus. If the person has a risk factor, he / she is not allowed to donate.
- Each blood donation is tested for known pathogens, for example: HIV, hepatitis B and hepatitis C. If a blood donation tests positive, it is not used. The donor can no longer donate blood.
- After the plasma is pooled, the plasma is again tested for known pathogens. If the plasma pool contains any trace of contamination, it is discarded.
- After manufacture, the final product undergoes a viral inactivation process. This is to kill any viruses which might be in the blood product. Methods of viral inactivation are: heating the clotting concentrate with vapour heat, treating the clotting concentrate with solvent detergents and nano-filtering. These viral inactivation methods are very effective in killing HIV, hepatitis B and C.

What are the blood products of choice for hemophilia A?

Genetically engineered (recombinant) factor VIII is the clotting factor concentrate used by Canadians with hemophilia A. It has been the product of choice since being introduced in 1993. The brand names used in Canada are Kogenate[®]FS, Advate[®], Helixate[®]FS and Xyntha[®]. In Quebec, Eloctate[®], an extended half-life product, was introduced in 2015 for patients with specific needs.

Plasma-derived factor VIII is sometimes used in particular situations for the treatment of hemophilia A: 1) for previously untreated patients who may be at higher risk for the development of inhibitors and 2) for immune tolerance induction for patients who have already developed antibodies to factor VIII. Brand names used in Canada are Humate P[®] and Wilate[®].⁴

Side effects of factor VIII^{5,6,7,8}

In patients who have had previous treatment with factor VIII, some side effects included reactions at the injection site, rash and itchy skin. In patients who had no previous treatment with factor VIII, some side effects included formation of inhibitors to factor VIII, reactions at the injection site, rash, and itchy skin.

Inhibitors, or antibodies, against factor VIII, may prevent it from working properly. If your bleeding is not controlled with the usual dose of factor VIII, call your hemophilia doctor or nurse. You should be monitored in order to find out whether a factor VIII inhibitor is present. Some other side effects include cold sensation, chest pain, rapid heartbeat, sweating, drowsiness, muscle weakness, loss of appetite,

⁴ Canadian Hemophilia Society. 2012. Factor replacement therapy. <http://www.hemophilia.ca/en/bleeding-disorders/hemophilia-a-and-b/the-treatment-of-hemophilia/factor-replacement-therapy/>

⁵ Baxter. 2010. Advate Product Monograph. Mississauga, Ontario: Baxter. Page 3

⁶ Behring. 2010. Helixate FS Product Monograph. Ottawa, Ontario: Behring. Page 27

⁷ Pfizer. 2011. Xyntha Solofuse Product Monograph. Kirkland, Quebec: Pfizer. Page 47

⁸ Bayer. 2011. Kogenate FS Product Monograph. Toronto, Ontario: Bayer. Page 28

muscle pain, pain, coughing, shortness of breath, diarrhea, stomach cramps, altered taste, injection site pain or inflammation and weakness.

You may find that more factor VIII product is required than estimated to stop the bleeding (lack of effect). If you are concerned about any possible side effects, talk to your doctor.

There is a possibility that you could have an allergic reaction. Allergic reactions may manifest with any of the following: rash, hives, itching, tightness of the chest, difficulty breathing, throat tightness, and/or low blood pressure (e.g. weak pulse, feeling lightheaded or dizzy when you stand, and possibly shortness of breath). If you experience any of these symptoms, stop the infusion and immediately phone your doctor or go to the Emergency Department. Should a significant increase in pulse rate occur during administration, reducing the rate of administration or temporarily halting the injection usually allows the symptoms to disappear promptly.

As with all factor VIII products, the clinical response may vary. If your bleeding is not controlled after infusing, contact your doctor immediately. Your factor VIII level may need to be measured by your physician who may recommend another dose in order to achieve a satisfactory clinical response. If your plasma factor VIII level fails to increase as expected or if bleeding is not controlled after adequate dosing, your physician may test for the presence of an inhibitor (neutralizing antibodies).

Call your hemophilia doctor or nurse right away if any side effect becomes serious, if you notice any side effects not listed, or if there is any other side effect that concerns you. Tell all your doctors, dentists, and pharmacists who are treating you about the factor VIII product that you are taking. If you are about to start taking any new medication, tell your doctor and pharmacist what factor VIII product you are taking.

If you become pregnant while taking any factor VIII product, tell your hemophilia doctor and your doctor who will look after you during your pregnancy.

This is not a complete list of side effects. For any unexpected effects while taking any factor VIII product, contact your doctor or hemophilia treatment centre. Contact your hemophilia doctor immediately if your bleeding does not stop as expected.

What are the blood products of choice for hemophilia B?

Recombinant factor IX, which goes under the brand name of BeneFIX® is the blood product used by most Canadians with hemophilia B. It was introduced in Canada on a regular basis in 1998. In Quebec, Alprolix™, an extended half-life product, was introduced in 2015 for patients with specific needs.

Plasma-derived factor IX is also used by Canadians with hemophilia B. The brand name used in Canada is ImmunineVH®.

Side effects of factor IX^{9,10}

⁹ Baxter. 1999. Immunine Product Monograph. Toronto, Ontario: Baxter. Page 4

¹⁰ Pfizer. 2011. BeneFIX Product Monograph. Kirkland, Quebec: Pfizer. Page 27

During your treatment, your blood will be checked for inhibitors to factor IX activity. Inhibitors are antibodies against factor IX, which are made by your immune system. The inhibitors stop the factor IX from working as well as it used to. Tell your doctor immediately if you are using increasing amounts in order to control a bleed.

Injection of any medicine intravenously may have side effects. Often they are not serious but sometimes they can be. You may need medical treatment if you experience some of the following serious side effects: skin rash, itching, chest tightness, wheezing, dizziness, hives, faintness, rapid heartbeat, shortness of breath, a swollen face, or blurred vision. It could mean that you are having an allergic reaction.

Tell your doctor if you notice any of the following side effects and they worry you: headache, runny or blocked nose, light-headedness, fever, chills, flushing, nausea, vomiting, diarrhea, feeling tired, drowsy or a lack of energy, discomfort or swelling at the injection site, altered taste, coughing, burning sensation in the jaw or skull, or changes in your vision.

These are all mild side effects of injection and will usually disappear on their own. Call your hemophilia doctor or nurse right away if any side effect becomes serious, if you notice any side effects not listed, or if there is any other side effect that concerns you.

Patients should be informed of the early symptoms and signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, dyspnea, wheezing, faintness, hypotension, drop in blood pressure, shock and anaphylaxis. Patients should be advised to discontinue use of the product and contact their physician and/or seek immediate emergency care, depending on the severity of the reaction, if these symptoms occur. In rare cases, replacement therapy with human blood coagulation factor IX concentrates may lead to the formation of circulating antibodies which inhibit factor IX.

This is not a complete list of side effects. For any unexpected effects, contact your doctor or hemophilia treatment centre.

How often are factor concentrates given?

Depending on the person, factor concentrates are given:

- every day
- several times a week
- several times a month
- only in cases of an accident or surgery or
- almost never

The hemophiliacs who receive factor concentrates the most often are:

- severe hemophiliacs
- children who are very active
- hemophiliacs on prophylaxis therapy.

What is prophylaxis therapy vs. on-demand therapy?

In prophylaxis therapy, hemophiliacs receive factor concentrates one or more times a week to prevent bleeding. The goal is to keep the levels of factor VIII or IX in the blood high enough that bleeding does not happen. This therapy is common with children with severe hemophilia.

On-demand therapy is the infusion of factor concentrates immediately after the beginning of a bleed. The goal is to stop the bleeding quickly, before any damage is done to the joint or muscle.

Research has shown that prophylaxis therapy gives children the best chance to reach adulthood without damage to their joints.

Are these blood products effective in stopping bleeding?

Yes, for most hemophiliacs, factor concentrates are very effective in stopping bleeding. Hemophiliacs can even have major operations without bleeding more than a person whose blood is normal.

However, some hemophiliacs' bodies reject the infusions of factor concentrates. They develop inhibitors. Inhibitors are the body's way of fighting off what it sees as a foreign agent. This means that as soon as the coagulation factor is injected, it is eliminated. This often happens before the factor concentrate is able to do its work and stop the bleeding.

Fortunately, there are ways to help most hemophiliacs who have inhibitors. (See the complications of hemophilia.)

Is factor replacement therapy always necessary for bleeds?

No. Minor bleeding episodes associated with hemophilia sometimes do not require medical treatment.

For example:

- small bruises usually disappear on their own
- bleeding from minor cuts can be stopped by applying pressure
- very minor bleeding into tissues can sometimes be treated by :
 - rest
 - elevation of the limb
 - applying ice to the site of the bleed.

Bleeding into a joint or a muscle (especially around the hip, calf or forearm) is never minor. Treatment with factor concentrates is essential.

Doctors say, 'When in doubt, infuse. Ask questions later.'¹¹

What other treatments are helpful to treat bleeding in hemophilia A and B? Desmopressin

¹¹ Canadian Hemophilia Society. 2012. Factor replacement therapy. <http://www.hemophilia.ca/en/bleeding-disorders/hemophilia-a-and-b/the-treatment-of-hemophilia/factor-replacement-therapy/>

Desmopressin is a synthetic drug which is a copy of a natural hormone. Desmopressin is not made from blood. Desmopressin is useful in treating people with mild or moderate hemophilia A. It is of no value for people with severe hemophilia A or with any type of hemophilia B.

It acts by releasing von Willebrand factor stored in the lining of the blood vessels. Von Willebrand factor is another protein which is important in blood clotting. One of its roles is to transport factor VIII in the bloodstream. Doctors think that by increasing von Willebrand factor levels, more factor VIII is brought to the site of damaged blood vessels.

Desmopressin can be taken in three different ways. It can be injected into a vein. Most often, the brand name for this kind of desmopressin is DDAVP; It can be injected under the skin. The brand name for this kind of desmopressin is often Octostim; and it can be taken by nasal spray. The brand name of the nasal spray is often Octostim Spray.

Desmopressin is usually effective for mild and moderate hemophiliacs. However, different people respond to desmopressin in different ways. Therefore, a doctor needs to do tests to find out each individual's response to the drug. Ideally, these tests are done before any urgent need for the drug, such as surgery.

Since desmopressin acts by releasing von Willebrand factor stored in the body, you cannot 'go to the well' too often. A sufficient amount of time, usually 24 hours, must elapse between doses of desmopressin to allow the body to rebuild its stores.

In serious bleeds or major surgery, desmopressin alone may not be enough to control bleeding. In such a case, a person should also receive a concentrate of factor VIII. (See What are the blood products of choice for hemophilia A?)

Desmopressin can sometimes have some mild side effects. These are:

- facial flushing
- mild headache
- nausea and abdominal cramps.

Desmopressin can make the body retain water. Therefore, doctors recommend that after receiving desmopressin people drink only enough fluid to satisfy thirst.

If a person has a very bad headache or has not been able to pass water 24 hours after taking desmopressin, he/she should go to the hemophilia / bleeding disorder clinic or emergency room for help.

Cyklokapron and Amicar

Cyklokapron (tranexamic acid) and Amicar (aminocaproic acid) are useful in treating both hemophilia A and B.

Cyklokapron and Amicar are drugs that help to hold a clot in place once it has formed. They act by stopping the activity of an enzyme, called plasmin, which dissolves blood clots.

They do not help to actually form a clot. This means they cannot be used instead of desmopressin or factor VIII or IX concentrate.

They can be used to hold a clot in place in mucous membranes such as the inside of the mouth; the inside of the nose; inside the intestines (the gut); and inside the uterus (the womb).

Cyklokapron and Amicar have proven very useful for people with hemophilia and for carriers who experience bleeding. They are used before dental work; when a person has mouth, nose and minor intestinal bleeding; and for carriers with heavy, prolonged menstrual bleeding.

These drugs come in tablet form.

Cyklokapron and Amicar can sometimes have some mild side effects. These are feeling sick to the stomach (nausea); feeling tired or sleepy; feeling dizzy; having loose bowel movements (diarrhea); and having pain in the stomach.

These mild side effects go away when a person stops taking the drugs or the doctor reduces the dosage.¹²

The complications of hemophilia

The most important complications are:

- the development of inhibitors. An inhibitor happens when the body's own immune system sees the factor concentrate as a foreign agent, and then destroys it.
- damage to joints as a result of repeated bleeds.
- blood-borne infections such as HIV, hepatitis B and hepatitis C, which were transmitted by factor concentrates in the past.¹³

For more information on hemophilia A & B, visit www.hemophilia.ca/en/bleeding-disorders/hemophilia-a-and-b/

¹² Canadian Hemophilia Society. 2012. Other treatments. <http://www.hemophilia.ca/en/bleeding-disorders/hemophilia-a-and-b/the-treatment-of-hemophilia/other-treatments/>

¹³ Canadian Hemophilia Society. 2012. The complications of hemophilia. <http://www.hemophilia.ca/en/bleeding-disorders/hemophilia-a-and-b/the-complications-of-hemophilia/>