FOREWORD

The B2B (hemophilia B patient to hemophilia B patient) series began in 2005 as a vehicle to empower individuals with hemophilia B through peer support and education. The objective of the program remains to address the various challenges of having hemophilia B, especially those encountered when transitioning from one life stage to another. Another goal of the B2B program is to help strengthen the internal support system and education network within the hemophilia B community. The B2B program is a sharing of firsthand accounts about everyday life from those living with hemophilia B.

The three previous B2B books, Speaking From Experience, A Guide for Mature Adults, and A Guide to the Preteen Passage, presented peer-to-peer life experiences from young adults and mature adults with hemophilia B. In the third book, families of preteens provided a “heads up” about the future when raising preteens with hemophilia B. The fourth B2B book in this series, Perspectives on Hemophilia B in Early Childhood, will offer tips from parents who have raised infants, toddlers, and preschoolers with hemophilia B, as well as insight from medical professionals who treat children with hemophilia B.

The views and opinions expressed in this book are those of an advisory board comprised of parents and hemophilia care specialists within the hemophilia B community and are not those held by Pfizer Inc.

The information in this booklet should in no way replace the advice of your health care professional. Be sure to talk with your doctor, nurse, or hemophilia treatment center (HTC) staff regarding any form of medical advice or treatment.
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INTRODUCTION

The early childhood years, from birth through age 6, often encompass a tremendous amount of developmental change for a child, beginning from day one of life, when an infant’s body movements are simple reflex actions. From that day forward, it may seem new physical and social milestones are reached daily as continuous muscle development takes place and increased alertness and curiosity occur.

The first 12 months of life can be an exciting time for parents/caregivers as they watch their infant change faster and work harder than imaginable. Parents/caregivers often begin to notice better and better muscle control appearing at about 6 months of age when an infant may start to move around on his or her own. By the end of the first year, the infant may stand without assistance and begin to become a sociable person, distinguishing familiar people from strangers. For the next few years, the toddler years, stages of development seem to come at a very fast pace, and for the parents/caregivers of a young child with hemophilia B, these stages of increased mobility and exploration can possibly result, either directly or indirectly, in a bruising or bleeding episode.

Dealing with a child’s hemophilia B can be challenging for any parent/caregiver. As children become more and more curious about the world around them, it will become more and more important that they are not kept from learning about their environment in an effort to protect them from bruising and bleeding.

Parents/caregivers may now find it tricky to manage the child’s needs with those of the other family members. Because parents are the most critical influence in a child’s life, it’s important that they be aware of how hemophilia B may affect them and the other family members emotionally, and how they can work to keep it from interfering with parenting/caregiving.

Fortunately, guidance and support are available to families of a child with hemophilia B through medical professionals, hemophilia treatment centers, and other families who have experienced like situations. With their help, parents/caregivers can learn how to cope with their child’s hemophilia B, how to meet their own needs and the needs of other family members, how to organize their time, and how to forgive themselves for not being perfect.
Hopefully, you will find this book and the listed resources to be invaluable support for you and your family, now and in the future, as you raise your child with hemophilia B.

The objectives of this book are to:

- Provide an overview of hemophilia B, including treatment issues and parenting/caregiving situations that may arise during early childhood years
- Offer recommendations from hemophilia B community members and medical experts for meeting the challenges of everyday living for your family and your child with hemophilia B
- Suggest resources for parents/caregivers of infants and toddlers with hemophilia B to help them manage specific psychosocial and/or treatment issues that may arise during this time
WHAT IS HEMOPHILIA?
Hemophilia is a congenital bleeding disorder. About 18,000 people in the United States have hemophilia and each year another 400 babies are born with the disorder. Hemophilia usually occurs only in males; however, there are exceptions.

The term bleeding disorder refers to a wide range of medical problems that lead to poor blood clotting and continuous bleeding. You may hear them referred to as coagulopathy, abnormal bleeding, or clotting disorders. A person with a bleeding disorder tends to bleed longer than someone who does not have a bleeding disorder.

Persons born with hemophilia have little or none of a protein needed for normal blood clotting. The missing protein is called a clotting factor, which works together with other proteins and platelets to help blood clot. Platelets are small pieces of blood cells that are formed in the bone marrow. When blood vessels are injured, clotting factors help the platelets stick together to plug cuts and breaks at the site of the injury to stop the bleeding. Without clotting factors, normal blood clotting cannot take place. When a person with hemophilia is injured, they do not bleed harder or faster than a person without hemophilia, they bleed longer. Hemophilia can range from mild to severe.

There are two main types of hemophilia:

- **Hemophilia A**—the most common type of hemophilia
  - The body has little or no clotting factor VIII
  - About 9 out of 10 people with hemophilia have hemophilia A
- **Hemophilia B**—the second most common type of hemophilia, is also known as factor IX deficiency, or Christmas disease
  - The body has little or no clotting factor IX
  - Hemophilia B occurs in about 1 in 25,000 male births

Factor deficiency disorders include those with deficiencies in factor I, factor II, factor V, combined factor V and factor VIII, factor VII, factor VIII (hemophilia A), factor IX (hemophilia B), factor X, factor XI (hemophilia C), and factor XIII.
There are different levels of hemophilia; each is based on the amount of clotting factor in the blood. People with normal blood have factor IX levels between 50% and 150%. Hemophilia is largely an inherited disorder, but it can also be acquired—it can develop during a lifetime if the body forms antibodies to the clotting factors already in the bloodstream. The antibodies can block the clotting factors from working.

- People with mild hemophilia (6% to 49% factor level) usually have problems with bleeding only after serious injury, trauma, or surgery. In many cases, mild hemophilia is not discovered until an injury or surgery or tooth extraction results in unusual bleeding. The first episode may not occur until adulthood.

- People with moderate hemophilia (1%-5% factor level), about 15% of the hemophilia population, tend to have bleeding episodes after injuries. They may also experience occasional bleeding episodes without obvious cause. These are called “spontaneous bleeding episodes.”

- People with severe hemophilia (less than 1% factor level), about 60% of the hemophilia population, have bleeding following an injury and may have frequent spontaneous bleeding episodes, often into the joints and muscles.

  - Severe hemophilia causes severe bleeding throughout life, usually beginning soon after birth. In some babies, hemophilia is suspected immediately with the appearance of a scalp hematoma after delivery or when a routine circumcision (removal of the foreskin of the penis) results in excessive bleeding. Toddlers are at particular risk because they fall frequently and may bleed into the soft tissue of their arms and legs. These small bleeds result in bruising and noticeable lumps, but do not usually require treatment. As a child becomes more active, bleeding may occur into the muscles, a much more painful and debilitating situation.

The age when hemophilia B is first diagnosed in a child, as well as the frequency of bleeding episodes the child experiences, is generally related to the factor IX clotting activity. In any affected individual, bleeding episodes may be more frequent in childhood and adolescence than in adulthood. This greater frequency is a function of both physical activity levels and vulnerability during more rapid growth.

There are several important considerations when caring for a person who has hemophilia. Prevention of bleeding episodes should be a primary goal. The second goal involves treating bleeding episodes early and aggressively. Additionally, supportive and adjunctive measures for each bleeding episode in the context of a multidisciplinary team approach should be used.
Standard treatment is infusion of factor IX concentrates to replace the defective clotting factor. The amount infused depends upon the severity of bleeding, the site of the bleeding, and the weight of the patient. 

The choices for treatment of hemophilia B include:

- Recombinant Factor IX Concentrate
- Plasma-Derived Factor IX Concentrate

Following an infusion, the doctor may perform a blood test to measure the level of circulating factor IX activity in a patient’s blood, also called recovery. Knowing this important recovery value helps the doctor figure out the proper dose of factor needed.

Factor IX recovery varies for each individual. It can be influenced by age and weight.

**What Are the Symptoms of Hemophilia B?**

An accurate diagnosis of hemophilia is the first essential step to hemophilia care.

Bleeding is the most common symptom of hemophilia, especially into the joints and muscles. When a child with hemophilia is injured, the child does not bleed faster than a child without hemophilia, just longer. He may also start bleeding again several days after an injury or surgery. For a child with hemophilia, small cuts or surface bruises are usually not a problem, but deeper injuries may result in bleeding episodes that could cause serious problems and lead to permanent disability unless treated promptly.
The symptoms of hemophilia bleeding depend on where the bleeding is occurring. Young infants may have bleeding from their mouth when they are cutting teeth or if they bite their tongue or tear tissue in their mouth.\textsuperscript{11}

Toddlers and older children commonly have bleeding into their muscles and joints. The symptoms of these types of bleeds include:

- Pain
- Swelling
- Loss of range of motion
- Inability to move or use the affected arm or leg

In joint bleeds there is usually no bruising or discoloration of the skin to indicate that the swelling and pain are due to bleeding.\textsuperscript{11}

Other symptoms of hemophilia include:

- Easy bruising; children may have many bruises of different sizes all over their bodies
- Prolonged nosebleed\textsuperscript{11}
- Vomiting of blood\textsuperscript{11}

In the majority of patients, hemophilia is diagnosed at birth because of a family history. In approximately one third of patients, the occurrence of hemophilia represents a new genetic event or mutation.\textsuperscript{11} The usual initial symptoms include easy bruising; oral bleeding, especially from a torn frenulum; hemarthrosis; and intramuscular hemorrhage. When hemophilia is suspected on the basis of either clinical findings or a positive family history, initial diagnostic studies may be done to confirm the diagnosis.\textsuperscript{13}

\textbf{MASAC Recommendations}\textsuperscript{12}

In 1954, the National Hemophilia Foundation (NHF) formed a medical advisory council comprised of scientists, physicians, and other treatment professionals who are regarded as experts in the field of bleeding disorders, to advance clinical care and promote hemophilia research. This group is now known as the Medical and Scientific Advisory Council (MASAC), and it establishes the quality-of-care guidelines for the treatment of hemophilia. The recommendations issued by MASAC are guidelines that are intended to set the standard of care around the world and are referred to by international physicians, medical schools, pharmacists, emergency room personnel, insurance companies, and others. The MASAC recommendations are posted on the NHF Web site: www.hemophilia.org.
Surgery can be a serious matter for anyone with hemophilia as excessive bleeding is always a concern. If your child needs to undergo elective surgery, there are a few things you should know.14

- Surgical procedures should be performed in coordination with a team experienced in the management of hemophilia.
- Procedures should take place in a center with adequate laboratory support for reliable monitoring of the clotting factor level.
- Preoperative assessment should include inhibitor screening.
- Surgery should be scheduled early in the week and early in the day for optimal laboratory and blood bank support, if needed.
- Availability of sufficient quantities of clotting factor concentrate should be ensured before undertaking major surgery for hemophilia.
- The dosage and duration of clotting factor concentrate coverage depends on the type of surgery performed.
It is often difficult to understand how your child can have hemophilia B when you, the parent, do not have hemophilia B. However, you may have been told that you are the carrier of the disorder.

Hemophilia B is a sex-linked disease passed on from a female to her male offspring. As previously discussed, hemophilia B is caused by a deficiency in factor IX, resulting from a genetic defect of the X chromosome.

We each have two chromosomes determining our sex: females have XX, and males have XY. Because the trait is carried only on the X chromosome, it is called sex linked. A female child always receives two X chromosomes and nearly always will receive at least one normal X chromosome. Therefore, even if she receives one abnormal X chromosome, she will still be capable of producing a sufficient quantity of factor IX to avoid the symptoms of hemophilia. Such a person who has one abnormal chromosome but does not actually suffer from the disease is called a carrier. She carries the abnormality that causes hemophilia and can pass it on to her offspring. If, however, she has a son who receives her abnormal X chromosome, he will be unable to produce the right quantity of factor IX, and he will suffer some degree of hemophilia (males inherit one X and one Y chromosome and, therefore, have only one X chromosome). In rare cases, a father with hemophilia and a carrier mother can pass on the right combination of chromosomes to result in a female child with hemophilia. Carrier females with factor IX clotting activity lower than 30% are at risk for bleeding that is usually comparable to that seen in males with mild hemophilia. However, more subtle abnormal bleeding may occur with baseline factor IX clotting activities between 30% and 60%.
Figure A  A father with hemophilia will pass the defective gene to his daughters, making them carriers. His sons, however, will not be affected because they get their X chromosome from their unaffected mother.1

Figure B  In a mother who is a carrier, there is a 50% chance her daughter will be a carrier also. If she has a son, there is a 50% chance he will have hemophilia because she has one “affected” X chromosome.1

About one third of all people with hemophilia B are the first member of their family to ever have the disease.15 These individuals have had an occurrence in the embryonic development stage of a spontaneous change that affected the X chromosome, resulting in hemophilia B. Once such a spontaneous change takes place, children of the affected person can inherit the newly created, abnormal chromosome.
THE IMPORTANCE OF COMPREHENSIVE CARE
What Is Comprehensive Care?

Comprehensive hemophilia care is a multidisciplinary team approach to treat the whole person, and the family, through continuous supervision of the medical and psychosocial aspects of the disease. This type of care addresses physical, emotional, educational, financial, and vocational needs. The hemophilia treatment center (HTC) is a comprehensive care facility where your child with hemophilia and your family will experience this type of care.16

To sufficiently offer comprehensive care, typical resources should include17:

- Patient registries
- Reference diagnostic services
- Established treatment protocols
- Direct psychosocial and educational services
- Consult for surgery support and blood-borne diseases
- Genetic counseling
- Research programs

The World Federation of Hemophilia (WFH) defines the functions of a comprehensive care program as one that18:

- Carries out all tests necessary for the definitive diagnosis of hemophilia and other inherited bleeding disorders
- Educates patients and parents regarding safety precautions for the prevention and early identification of bleeds
- Manages bleeding episodes with appropriate treatment products and first aid
- Promotes regular exercise to maintain muscle and joint health and provides rehabilitative services for restoring function following bleeds
- Develops and reviews a management plan for each patient
- Monitors and manages the complications of hemophilia and its treatment, such as arthropathies, inhibitors, and transfusion-transmitted infections
• Provides genetic counseling and genetic diagnostic services for patients and family members
• Educates, advises, and counsels patients, family members, health care workers, educators, and employers to ensure that the patients’ needs are met
• Conducts research to further knowledge and improve the management of bleeding disorders, often conducted in collaboration with national and international hemophilia research centers

Comprehensive care has resulted in significant improvement in the health of persons with hemophilia, as well as reducing the amount of health care utilization. A Centers for Disease Control and Prevention (CDC) study of approximately 3,000 people with hemophilia A and hemophilia B showed that those who used an HTC were 30% less likely to die of hemophilia-related complications compared with those who did not receive care at an HTC.19

The focus of the comprehensive care team at the HTC is the prevention of severe and costly medical complications, such as progressive joint disease. The members of the team are committed to assisting patients and families with diagnosis and assessment. They also help with education, management of acute bleeding episodes, initiating and providing home infusion therapy, routine follow-up, and preoperative and postoperative management when surgery becomes necessary.

Finding an HTC
To take advantage of the services at an HTC, register at one near you. To find an HTC near you, contact handi@hemophilia.org.

The Hemophilia Comprehensive Care Team
Many of the HTCs are located at major university medical and research centers and offer hemophilia treatment teams consisting of20,21:
• Pediatric/adult hematologists (doctors who have expert knowledge about hemophilia and other bleeding disorders)
• Nurse coordinators (play a key role and serve as a link between the family and the HTC comprehensive team members)
• Social workers (provide support to patients and families, and assist in identifying barriers to care and strategies to improve access to care)
Physiatrists (physical therapist specialists who analyze the impact of the disease on body functions and structures and assess the functional abilities of the patient in activity, exercise, and rehabilitation)

Dentists (work closely with the HTC team by providing routine checkups and oral hygiene)

Orthopedists (doctors who specialize in managing joint disease resulting from repeated bleeding episodes)

Occupational therapists (assist in maintaining activities of daily living)

Laboratory services (essential in performing blood and other laboratory tests to determine the type and severity of the bleeding disorder, measure factor levels, check for the presence of inhibitors)

Genetic counselors (provide education and information regarding the inheritance pattern of the disorder)

You and your child are also members of the treatment team. The staff at the HTC needs your input to develop a plan of care that will help keep your child healthy, active, and able to live successfully with the challenge of hemophilia.

Many families utilize the resources provided by HTCs because the staff understands their unique needs and takes the time to develop treatment plans. State-of-the-art medical care is provided and many benefit from the skills and experiences provided by the team.

A network of 140 federally funded HTCs across the country offers excellent treatment, education, and support services to individuals with hemophilia and their families.
Do the 5!

“Do the 5!” — the theme of the National Prevention Program (NPP) — is a simple, helpful way to remember some of the most important things you can do to take care of your child.22

“Do the 5” is a collaborative effort by the National Hemophilia Foundation, CDC, treatment centers, and members of the bleeding disorders community.23

What Are the “5”?22

1. Get your child an annual, comprehensive checkup at a treatment center.

2. Get your child vaccinated (hepatitis A and hepatitis B are preventable through vaccination).22

3. Treat bleeds early and adequately.22
   – Learn to recognize the early signs of a bleed and learn to recognize which bleeds may be serious.24
   – Be prepared by having factor readily available at all times whether you infuse your child or you take it with you to the emergency room (ER).24

4. Have your child exercise to maintain a healthy weight and protect the joints (speak with your doctor about the type of exercise program that would be right for your child).22

5. Get your child tested regularly for blood-borne infections.22
Kim S is a hemophilia nurse who believes that families living with hemophilia should make participation at an HTC part of their regular care. A Centers for Disease Control and Prevention (CDC) study of approximately 3,000 people with hemophilia A and hemophilia B showed that those who used an HTC were 30% less likely to die of a hemophilia-related complication compared with those who did not receive care at an HTC.

Kim also reminds us of the NHF “Top 10 Reasons to Get an Annual Comprehensive Checkup at an HTC”:26*

1. (Help live) longer, healthier lives
2. Early detection of complications
3. Fewer hospitalizations
4. Home infusion instruction
5. Physical therapy and an exercise plan designed for the patient
6. Participation in research studies
7. Treatment and specialized lab tests
8. Coordinated care and advocacy for added services
9. Counseling and support
10. Blood safety testing and monitoring

* This data is from 2001.
HTCs not only provide comprehensive care through a treatment team, they also emphasize prevention services to help reduce or eliminate complications. Some of these services include using preventive medicine and connecting patients with community groups that provide education and support to families.

**Travel Assistance**

Kim’s staff at the HTC is prepared to help with travel preparations as well. Staff members contact the HTC in your travel destination and make sure all necessary information about your child’s care is available to the center staff through a “travel letter.” You carry this letter with you on your trip and show it to any other HTC that your child may need to visit while away.

Travel can be challenging for anyone today, but especially for those needing to travel with medications and supplies. The following tips can help to prepare for security screening at an airport:

- Pack your child’s medications in a separate pouch/bag to simplify the inspection process.
- Make sure that all of your child’s medications are clearly identified. Do not pack factor in your checked baggage.
- Factor products should never be packed in checked baggage because their glass containers could break due to temperature fluctuations.
- If you are planning an extended stay and a large amount of factor will be needed, have your home care company send factor to your destination ahead of your visit.

To learn more about security measures specific to travelers with disabilities and medical conditions, contact the Transportation Security Administration by visiting www.tsa.gov or calling 1-866-289-9673. You can also visit www.hemophilia.org for air travel recommendations specific to the bleeding disorder community.
MANAGING YOUR CHILD’S HEMOPHILIA B DURING EARLY CHILDHOOD
Infancy is a spectacular time of life. During the first 12 months of life, your baby will change faster and work harder than at any other period in his life. The infant has so much to learn: to reach, to grasp, to recognize, to smile, to laugh, to roll over, to sit, and to maybe even stand alone and walk. These are just a few of the things your baby will work at doing before the end of the first year.27

Parents/caregivers are the most critical influence in a baby's first year of life. The parent/caregiver is the primary nurturer, teacher, and protector. The quality of parenting/caregiving and the interactions between parents/caregivers and baby in the earliest weeks substantially determine how far development in the first year will progress. Clearly, children whose environment allows them to develop to their fullest intellectual potential and provides a happy, stimulating, and healthy childhood in which the capacity to love and to be loved is rewardingly learned will fare the best.27

How Will the Sequence of Stages in Development That Occurs in All Infants Affect Your Child With Hemophilia?

Parents/caregivers of a child with hemophilia may find it easier to care for the child if they understand the stages of physical, emotional, and mental growth all children go through. The sequence is mostly the same for everyone, but the timing is purely personal.27

Development follows a head-down-to-toes direction. Eye muscles come under control first, then the facial muscles, neck muscles, and the trunk and the legs. At this same time, a center-outward development is occurring in the fingertip direction.27 When your child is about 6 months, all of these components may begin to come together and your child may become more and more mobile, which is likely to increase the chances for bruising or bleeding. Your child may begin crawling, getting up on his hands and knees, and even standing while holding onto something. While it is important that you allow your child to explore and expand this newly acquired mobility, it’s also important that the environment is safe. This will be a challenging time for you, as your tendency may be to be overprotective.

The following is an overview of developmental milestones for infants, toddlers, and preschool children. Knowing ahead of time what to expect as your child with hemophilia grows may help you to gauge the types of safety measures that you may want to put in place during these life stages.
Developmental Milestones
Infants: Ages 6 to 12 Months

Gross Motor
- Voluntary crawling begins
- Turns, twists in all directions
- Rolls from back to stomach
- Creeps, propels self on tummy
- Stands with substantial support

Social
- Alternates hand with object in mouth
- Turns when he hears name
Special Considerations

Crawling and walking are important for muscle development despite possible increased bleeding.

Strong muscles help to protect joints and decrease joint bleeds.

Frequent use of playpens is discouraged.

Seldom have bleeding episodes in the first year.

May experience more bruising than other infants.

Head injuries should be reported to doctor immediately.

Safety Measures

Enroll child in MedicAlert® system; to order an emblem (bracelet or necklace for older children) call MedicAlert at (800) 432-5378.

Always use a car seat.

Never leave infant alone in bathtub, on a bed or changing table.

Put gates across stairways.

Keep stairways free of objects so you won’t fall while carrying baby.

Remove sharp or breakable utensils from lower cupboards.

Use a highchair with a strap and with a broad base.

Baby walkers can be dangerous and should not be used.

Avoid tablecloths that hang over the side of the table.


MedicAlert is a registered trademark of MedicAlert Foundation.
Developmental Milestones
The Toddler Years

Gross Motor31*
- Cruises about while holding on to an object or person
- Walks when supported
- Can pull self up to standing position
- Steps off low object
- May begin walking without support, but clumsy at running and climbing, requires watching
- Gets self to stand by flexing knees
- Standing, pivots body 90 degrees
- Walks, but prefers crawling
- Climbs up and down stairs
- May climb out of crib or playpen

Social31*
- Expresses emotions and recognizes them in others
- Distinguishes self from others
- Mimics actions of others

* As recommended from The First Twelve Months of Life by Theresa Caplan, copyright © 1993 by Theresa Caplan. Used by permission of Perigee Books, an imprint of Penguin Group (USA) Inc.
Special Considerations

- More prone to accidents due to increased mobility and lack of judgment
- Mouth and soft tissue bleeds are common
- Head bumps are common
- Head injuries need to be reported to physician immediately
- Visits to pediatrician and emergency room may become more frequent
- May associate infusion with something he has done or view it as a punishment
- Good time to explain to child that infusions will make him feel better
- Child should be praised when he reports symptoms
- Parents’ anxiety about bleeds may cause them to be overprotective

Safety Measures

- Lower child’s crib mattress to its lowest level to discourage climbing out of crib; also keep large stuffed animals out of crib as they can be used as stepping stones
- Discourage unsupervised climbing and jumping off high places or furniture
- Gates can be removed from stairway once toddler demonstrates he can negotiate stairs safely
- Use an approved car seat until child weighs 40 pounds and a booster seat for child weighing up to 80 pounds. Check your state law
- Tape or glue foam pads to the sharp edges of counters and coffee tables or remove coffee tables while child is learning to walk
- Place nonskid strips on floor of shower or bathtub
- Sew padding into the knees and seat of toddler’s pants to reduce bruising
- Make sure toddler wears shoes to protect feet; high top sneakers provide good ankle support
- Athletic elbow and knee pads help to protect against joint bleeds caused by falls
- Consider getting child a Big Wheel tricycle (generally more stable and closer to ground than regular tricycles)
**Developmental Milestones**

The Preschool Years

**Gross Motor**
- Walks with an agile, almost adult style
- Runs around obstacles
- Running is more controlled, can start, stop, and turn
- Turns somersaults; hops on one foot; gallops
- Can easily catch, throw, and bounce a ball
- Catches large balls and throws overhead
- Climbs ladders; uses slide independently
- Rides a tricycle
- Alternates feet when climbing stairs
- Can brush teeth, comb hair, wash, and dress with little assistance

**Social**
- Follows simple directions; enjoys helping with household tasks
- Begins to recognize own limits
- Likes to play alone, but near other children
- Can now make choices between two things
- Begins to notice other people’s moods and feelings
- Thinks literally; starting to develop logical thinking
- Expresses anger verbally rather than physically
- Distinguishes right from wrong, honest from dishonest, but does not recognize intent
Special Considerations

- Begins to understand infusions are necessary to relieve pain
- Encourage child to report symptoms of a bleed
- Child may dislike venipuncture and not tell parents or staff
- Parents must patiently explain that infusions help with pain
- Praise child when he reports a bleed
- Child should be encouraged to participate in his care
- Helpful for medical staff to explain what is being done and to name equipment used
- Child can participate in medical care by choosing a venipuncture site, dissolving factor, holding pressure on the site, etc
- Flossing may cause a small amount of blood to ooze from gums at first, but as gums get healthier, oozing stops

Safety Measures

- Ice helps to reduce bruising and ease discomfort
- Make sure child wears helmet when roller skating, cycling, etc
- Avoid physical activity that involves rough body contact such as wrestling and hockey
- Help your child stay fit and trim; extra weight puts stress on joints
- NHF recommends that your child receive the hepatitis B vaccine (recommended for all children) and the hepatitis A vaccine (above 2 years old)
- Teach child to floss regularly and to brush teeth with a soft brush
- Inform dentist of child’s hemophilia
- Let your child know what to expect from an upcoming event or activity so he can prepare
RECOGNIZING AND TREATING BLEEDS IN EARLY CHILDHOOD
What Are the Types of Bleeds?

Hemorrhages or “bleeds” may be caused by injury or may occur spontaneously (without any apparent cause).[^34] Bleeds can begin in infancy, childhood, adolescence, or adulthood.[^4] The most common types are deep bleeding into the joints and muscles.[^13]

Newborn males may bleed following circumcision (removal of the foreskin from the penis).[^4][^13] During infancy, one of the most common bleeding signs is easy bruising.[^13] Another common place where bleeding can occur is in the mouth when biting the tongue[^4] or injuring the small piece of skin that attaches the center of the lips to the top and bottom of the mouth (the frenulum).[^4][^13] Infants with hemophilia may also bleed under the skin or into the muscle after getting a shot or injection.[^4]

During the toddler years, when children begin to move around more and more, they may experience bleeds into their joints. These types of bleeds are called hemarthroses, and they often occur in the knees, elbows, and ankles.[^13] These bleeds happen less frequently in the shoulders, wrists, and hips.[^4]

Minor head bumps can be frustrating because it’s hard to know whether to treat with clotting factor or not. Head bumps are especially common in young children at the toddler stage (ages 1 to 2 years) who are just learning to walk and run and who are unsteady on their feet. These children often bump into doors, walls, and furniture. Many times the child is not upset by the injury—he doesn’t even cry—and often there is no bruise or cut caused by the bump. If you are not sure, you should speak to the nurse coordinator or medical director of your child’s HTC.[^34]

If any of the following symptoms occur, you must seek medical assistance immediately: headache, blurred vision, nausea or vomiting, mood or personality changes, drowsiness, loss of balance or coordination, weakness or clumsiness, stiffness of the neck, loss of consciousness, or seizures.[^34]
R.I.C.E.

Bleeds in the joints, muscles, or soft tissues can be treated by using a form of first aid called R.I.C.E. (Rest [“R” can also mean Replacement of clotting factor], Ice, Compression, Elevation).

During a bleed, the affected area should be rested—no walking if the bleed is in the knee, no lifting if the bleed is in the elbow. To lessen pain or swelling, apply ice to the affected area—10 to 15 minutes every 2 hours is recommended. Applying pressure (compression) to the area can also help to slow the bleeding—such as using an elastic bandage. Always check with your local HTC for the proper way to apply the bandage. Elevating or raising the injured limb (arm or leg) above the heart will help to slow the bleeding.

It is always a good idea to check with a doctor if there are any questions about how to control a bleed.

For more details about appropriate activities, see the section “Complete List of NHF-Rated Sports and Activities” on page 56.
Serious Bleeds

The five major sites of bleeding episodes in hemophilia that threaten life, limb, or function are:

- Intracranial, or head bleeds
- Neck or throat bleeds
- Abdominal bleeds
- Kidney or bladder bleeds
- Ocular (eye) bleeds

All of these bleeds require a call to your doctor, immediate intervention, or a trip to your local emergency room.35

Other Bleeds

Some bleeds may require medical attention and others may not. Please speak with a medical professional to learn when to seek medical care.

Urinary Tract Bleeds4,34
About 66% to 90% of people with hemophilia have bleeding in the urinary tract, also called hematuria, at least once in their lives. A symptom to watch for includes reddish-brown urine.

Iliopsoas Bleeds4
Iliopsoas bleeds occur in the muscle of the pelvic area, near the hip joint. This type of bleed can damage the nerves of the thigh muscle, thereby limiting a person’s movement. If an iliopsoas bleed is left untreated, it can cause heavy blood loss and permanent damage.

Compartment Bleeds
Compartments are closed-in spaces, such as in the forearm muscles. When a person bleeds deep inside these closed spaces, the blood settles in this area and puts pressure on the nerves and blood vessels within the muscle. If left untreated, compartment bleeds can cause permanent nerve damage and sometimes a loss of limb.4 Symptoms to watch for include pain and tingling in the fingers or toes.34
**Mouth Bleeds**

If and when a child has a mouth bleed, it may be difficult for a clot to form. The inside of the mouth is wet and always moving. Because of this, it is difficult for an injury to heal. If a clot does form, it may fall out before the injury is healed. Speak with a doctor if this happens.

**National Hemophilia Foundation**

Publications from the National Hemophilia Foundation contain informative resources for people with bleeding disorders and their families. The list of available publications can be accessed at www.hemophilia.org.

**Bruising**
Bruises are another common bleeding symptom in people with hemophilia. Some bruises can be mild and heal on their own with ice, and others may not. Please seek medical attention for bruises that are very painful, grow larger over time, limit movement, or affect sensitive critical areas.

**Mouth Bleeds**
Mouth bleeds are a common occurrence in the infant and toddler age group. This type of bleed can be caused by teething and may begin in a child as young as 3 months. The emergence of baby teeth can be uncomfortable for a child. The child may chew or bite anything within reach, such as toys, in an effort to feel better. Chewing on toys can cut the gums and cause them to bleed. Often the bleeding can be kept under control by applying pressure to the area for 5 to 10 minutes. (This may not be an easy task, as the mouth of an infant or toddler is very small and the child may not cooperate.) If the bleeding does not stop, call the child’s health care provider.

Mouth bleeds, such as those caused by biting the lip or tongue, a torn frenulum, new teeth coming in, or a dental procedure, are very common in people with hemophilia. They can be very serious because persistent mouth bleeding can cause severe anemia.
Preparing for Emergencies

It can be difficult for patients with hemophilia to achieve and maintain a normal level of factor to prevent all potential hemorrhages. People with hemophilia are at risk for severe bleeding that may lead to serious or life-threatening circumstances requiring emergency care.36

People with hemophilia B, or parents of children with hemophilia B, are in the best position to manage their health or their child’s health.

- Learn as much as possible about hemophilia
- Learn what to do if a bleeding situation may be happening

Health care professionals in the ER will ask to be provided with information on the hemophilia patient’s past and current medical history. Be prepared to answer their questions.

Keeping an Infusion Log

It’s a good idea to keep an infusion log of your child’s treatments, including dates and times of the infusions, as well as emergency visits to the hospital. Make sure to include the site of the bleed, the date and time of the infusion, the child’s weight, how much factor was infused, and the side effects, if there were any. Bring this infusion log to the doctor when you and your child visit the HTC or an emergency room, as it will help to speed up care and also may be needed by your insurance company.

See “Sample Infusion Log” on page 42.
Be sure to write the date and time for each infusion.

Place the vial stickers here so you have a record of the lot number, expiration date, and the number of units per vial.

Describe how long after the bleed your treatment began. You can also note if you had any reaction to the factor.

Write down the units in each vial and the number of units used. This tracks how much factor was needed for each bleed.

Check the reason for your infusion.

---

**Sample Infusion Log**

<table>
<thead>
<tr>
<th>Date ____________</th>
<th>Time __________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight _____</td>
<td>Product _____________</td>
</tr>
<tr>
<td>Place stickers here</td>
<td></td>
</tr>
<tr>
<td>Total # units ______________</td>
<td></td>
</tr>
</tbody>
</table>

**Reason for infusion**

- _____ Prevention Activity/Event __________
- _____ Bleed/Injury Location____________
- _____ Bleeding Symptom(s) ______________
- _____ Follow-up Scheduled _____________

**NOTES**

________________________________________
________________________________________
________________________________________
________________________________________
Be Proactive When Treating Hemophilia B in Early Childhood

Thomas Truncale, DO, MPH, CIME
Associate Professor of Medicine
Department of Environmental and Occupational Medicine
University of South Florida
Parent of two sons with hemophilia

Thomas Truncale, DO, MPH, CIME, is a pulmonary and critical care physician at the University of South Florida. He and his wife have four children (three boys and a girl). Two of their sons have hemophilia: a 10-year-old and a 9-month-old. There is no family history of hemophilia that they have been able to identify, and his wife has three brothers. Their 10-year-old son was first diagnosed with hemophilia when he was 15 months old and beginning to walk. Dr. T points out that in most cases, infants don’t show signs of hemophilia until they are older and starting to become more mobile. At that time, bruising and joint swelling may appear and hemophilia may become apparent.

As a parent of children who have hemophilia, Dr. T has made several observations. With infants, toddlers, and preschoolers, he notes that nail clipping is an area where oozing might be noticed if the skin is accidently cut. He also cautions that any head bump or head injury can be a serious issue, especially if an abnormal appearance or odd behavior is noticed in the child. “At the very least, the physician should be called or the child taken to the emergency room.” This is also the case if the child has a catheter and develops a fever. If this should happen, the child should immediately be taken to the hospital. Dr. T stresses the importance of discussing any concerns or questions regarding your child’s care with your physician.
As a parent, Dr. T ranks proactivity number one in managing hemophilia in treatment, education, and parenting. With both of his sons, as soon as the children became active, they began discussions with the physician about the best treatment plan. They immediately sought out a source for comprehensive care, such as an HTC, where they could find all of the resources they needed, including physicians, nurses, social workers, dentists, and other families who had experienced the same challenges. Dr. T recommends locating an HTC that you can take your child to on a regular basis for medical care. “Regularity is very important,” advises Dr. T, “Establish a method of doing things and stick to it. Develop an association with the home care nurse and have both parents learn infusion. Infusion treatment requires a lot of stuff. Set aside a specific area in the home for the treatment where all of the supplies can be kept organized and ready for use. Check expiration dates on all medicines constantly. Provide a separate refrigerator for the medicines so they are not mixed in with food. Maintain regularity in this space.”

Proactivity should extend beyond the home into the day care center, preschool, church, and community. Dr. T recommends that all families of a child with hemophilia put together a package of educational materials for the school nurse, the teachers, church personnel, babysitters, and other families. The information in the package should include a personal card with important contact information. Most hemophilia treatment centers have educational materials available for this purpose. Don’t forget to add your own contact information to this package.
Your Personal Business Card

Prepare a personal business card to distribute to any people your child may come in contact with, such as parents of friends, relatives, teachers, church staff, sports staff, day care staff, sitters, and HTC personnel. Make sure to include your phone numbers (all of them) and other family phone numbers, as well as your child’s doctors' numbers and HTC personnel numbers.

<table>
<thead>
<tr>
<th>E M E R G E N C Y  C O N T A C T  C A R D</th>
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</thead>
<tbody>
<tr>
<td><strong>Jane Mother</strong></td>
</tr>
<tr>
<td>732.272.1234 (cell)</td>
</tr>
<tr>
<td>732.272.1234 (home)</td>
</tr>
<tr>
<td>732.272.1234 (office)</td>
</tr>
<tr>
<td><strong>Joe Father</strong></td>
</tr>
<tr>
<td>732.272.1234 (cell)</td>
</tr>
<tr>
<td>732.272.1234 (home)</td>
</tr>
<tr>
<td>732.272.1234 (office)</td>
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<tr>
<td><strong>Relative</strong></td>
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<tr>
<td>732.272.1234 (cell)</td>
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<tr>
<td>732.272.1234 (home)</td>
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<tr>
<td>732.272.1234 (office)</td>
</tr>
<tr>
<td><strong>Dr. Sam Physician</strong></td>
</tr>
<tr>
<td>732.272.1234</td>
</tr>
<tr>
<td><strong>HTC PERSONNEL</strong></td>
</tr>
<tr>
<td>Sam Nurse</td>
</tr>
<tr>
<td>732.272.1234 ext. 413</td>
</tr>
<tr>
<td>Joe Nurse</td>
</tr>
<tr>
<td>732.272.1234 ext. 415</td>
</tr>
<tr>
<td>Susan Nurse</td>
</tr>
<tr>
<td>732.272.1234 ext. 411</td>
</tr>
</tbody>
</table>
**How Will You Recognize an Emergency Situation?**

There may be no visible signs of bleeding in a person with hemophilia, but bleeding issues such as joint hemorrhages, head injuries, muscle bleeds, and trauma can be serious. Emergency bleeding events require recognition and immediate intervention with factor replacement products to replace the missing factor (factor IX) in the blood and restore normal blood clotting.  

The following situations typically require factor replacement therapy:

- **Any signs or symptoms of bleeding in the brain. Such bleeding is life-threatening and requires immediate emergency care**
- Suspected bleeding into a joint or muscle
- Significant injury to the head, neck, mouth, or eyes, or evidence of bleeding in those areas
- New or unusual headache, particularly one following trauma
- Severe pain or swelling at any site
- Open wounds requiring surgical closure, wound adhesive, or steri-strips
- History of an accident or trauma that might result in internal bleeding
- Invasive procedure or surgery
- Heavy or persistent bleeding from any site
- Gastrointestinal bleeding
- Acute fractures, dislocations, and sprains
- Limited motion, pain, or swelling of any joint
What to Take With You When You Go to the Emergency Room

- Clotting factor IX and infusion supplies
- For a joint bleed, an ice pack (if readily available) to begin icing the bleeding joint immediately
- Physician’s phone number in case the ER personnel need to speak to him or her
- Information about hemophilia B—the ER staff may have little experience with hemophilia B and may ask you about your child’s treatment
- Your child’s infusion log (if readily available)

Note: You may also want to carry a letter from your child’s physician describing your child’s hemophilia and their treatment. It’s also a good idea to find out in advance where to go for care when you are out of town.
Important Points to Remember When Emergency Care Is Needed

- Factor IX replacement therapy is used in patients with hemophilia B for acute bleeding episodes or presumed acute bleeding episodes

- Have an emergency dose of clotting factor concentrate in your home at all times
  - Clotting factor concentrates might not be kept on hand at all hospitals. If you do not have factor with you, the ER personnel may have to identify another hospital to best deal with the emergency. This will increase the time it takes until treatment is provided

- Take your child’s factor IX with you when you travel and/or if you go to the ER
  - The ER may ask you if you have your child’s factor IX with you, and they may ask you to infuse the dose for your child
Helping Your Child to Eat Right

Part of staying fit includes eating right—eating a well-balanced diet that includes plenty of fresh fruits and vegetables. Check with your local HTC for more information about nutrition. Maintaining a healthy weight is important for anyone with hemophilia, not just children. Being overweight can put additional pressure and stress on joints, such as knees and ankles. The additional pressure and stress can cause damage to the padding between the joints, or cartilage. For additional information about nutrition, visit www.health.gov/dietaryguidelines.

Staying Fit

Maintaining physical activity is important for all children. It is especially important for children with hemophilia, because building strong muscles can help protect joints from bleeds. Exercise helps to build strength and flexibility, both of which aid in preventing injuries. It is also good for the mind and assists in building a child's confidence. Taking part in sports can teach teamwork and develop self-esteem. Exercise develops healthy lifestyle habits that can be carried through a person's life. There are limitations, however, because some activities might be risky to a person with hemophilia.39,40

It's important to consult a doctor before participating in any sports activity.
**Complete List of NHF-Rated Sports and Activities**

Activities have been divided into 5 ratings based on a scale of 1 to 3:

<table>
<thead>
<tr>
<th>Safe (1)</th>
<th>Moderate – Dangerous (2.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>aquatics</td>
<td>basketball</td>
</tr>
<tr>
<td>archery</td>
<td>baseball</td>
</tr>
<tr>
<td>elliptical machine</td>
<td>canoeing</td>
</tr>
<tr>
<td>fishing</td>
<td>cheerleading</td>
</tr>
<tr>
<td>BMX racing</td>
<td>gymnastics</td>
</tr>
<tr>
<td>boxing</td>
<td>ice skating</td>
</tr>
<tr>
<td>diving (competitive)</td>
<td>horserace riding</td>
</tr>
<tr>
<td>football</td>
<td>in-line skating</td>
</tr>
<tr>
<td>hockey (field, ice, street)</td>
<td>jet skiing</td>
</tr>
<tr>
<td>hockey (field, ice, street)</td>
<td>karate</td>
</tr>
<tr>
<td>lacrosse</td>
<td>kung fu</td>
</tr>
<tr>
<td>motorcycling</td>
<td>mountaine biking</td>
</tr>
<tr>
<td>motorcross racing</td>
<td>scooter</td>
</tr>
<tr>
<td>rock climbing</td>
<td>snowboarding</td>
</tr>
<tr>
<td>(outdoor)</td>
<td>(nonmotorized)</td>
</tr>
<tr>
<td>scooter</td>
<td>skiing (downhill)</td>
</tr>
<tr>
<td>tennis</td>
<td>skiing (telemark)</td>
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<tr>
<td>ultimate Frisbee® disc golf</td>
<td>softball</td>
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<tr>
<td>yoga</td>
<td>snowboarding</td>
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<tr>
<td>Tai chi</td>
<td>softball</td>
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<tr>
<td>walking</td>
<td>soccer</td>
</tr>
<tr>
<td>weight lifting/ resistance training</td>
<td>surfing</td>
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<tr>
<td>weight lifting/ resistance training</td>
<td>tae kwon do</td>
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<tr>
<td>weight lifting/ resistance training</td>
<td>track and field</td>
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<tr>
<td>weight lifting/ resistance training</td>
<td>ultimate Frisbee® disc golf</td>
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<tr>
<td>weight lifting/ resistance training</td>
<td>volleyball</td>
</tr>
<tr>
<td>weight lifting/ resistance training</td>
<td>waterskiing</td>
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<table>
<thead>
<tr>
<th>Safe – Moderate (1.5)</th>
<th>Dangerous (3)</th>
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<tbody>
<tr>
<td>biking</td>
<td>BMX racing</td>
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<tr>
<td>body sculpting</td>
<td>boxing</td>
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<tr>
<td>circuit training</td>
<td>diving (competitive)</td>
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<tr>
<td>Frisbee® disc golf</td>
<td>football</td>
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<tr>
<td>pilates</td>
<td>hockey (field, ice, street)</td>
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<tr>
<td>rowing machine</td>
<td>lacrosse</td>
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<tr>
<td></td>
<td>motor cross racing</td>
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<td></td>
<td>rock climbing (outdoor)</td>
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<td>rodeo</td>
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<td>rugby</td>
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<td></td>
<td>scooter (motorized)</td>
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<td>snowmobiling</td>
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<td></td>
<td>trampoline</td>
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<td></td>
<td>weight lifting/ power lifting</td>
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<td></td>
<td>wrestling</td>
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The National Hemophilia Foundation does not recommend any sports activities rated 3 for people with bleeding disorders.

Activities rated 1 to 2 indicate the benefits outweigh the associated risks.

Frisbee is a registered trademark of Wham-O, Inc.
FINDING THE RIGHT DAY CARE OR PRESCHOOL
When considering child care, it is important to know the kinds of care available in your community. Remember, your child is a person who has a bleeding disorder. When choosing a center, keep in mind your child’s habits, personality, needs, likes, and dislikes; these needs are similar to those of the child’s peers who do not have a bleeding disorder. Gather as much information as possible about a child care center before choosing a program. You will want to consider whether to have someone come to your home (e.g., a nanny, relative, or au pair) or choose a child care setting near your home or work. Needless to say, how much the family can afford for child care influences, or even controls, your choice. When you are ready to look for care—whether an in-home babysitter, a family day care home, or a center-based program—talk with relatives, friends, neighbors, and coworkers. They are likely to know about resources in the community. They may even have recommendations for specific providers. Remember, your HTC and local NHF chapter can link you to other families who have young children with bleeding disorders, and they may have helpful advice.41
Resources for Finding Out-of-Home Child Care

There are several different types of child care programs. These include:

- Licensed child care homes (e.g., family day care homes) are homes that may be licensed to care for a limited number of children of varying ages.

- License-exempt child care (e.g., a family home where a parent is allowed to care for one or two unrelated children in addition to his or her own; also, governmental, university, church, synagogue, public school, and hospital-based programs).

- Center-based child care (e.g., group care where there is trained and paid staff).

To find out about programs where you live, contact:

- Child Care Aware, a program of the National Association of Child Care Resource and Referral Agencies (NACCRRA) at 1-800-424-2246. Child Care Aware also has a Web site: www.childcareaware.org.

To check on licensing of these facilities, call your Department of Children and Family Services, Department of Public Welfare, Department of Public Health, or your school district office.
Helping Day Care or Preschool Staff to Understand

In a child care facility, it is likely the caregivers will, at first, feel nervous about their responsibility for your child. Provide as much information about your child’s bleeding disorder as you believe is necessary for his safety. Be open to answering questions, even those that are asked over and over. Remember that most people know little or nothing about bleeding disorders.41

Make sure that the person in charge knows what to do if your child should become injured. Ensure that this person has a general understanding of what hemophilia is and the type(s) of bleeds your child may have. Write down all instructions you believe are important, and advise the person NOT to give your child any prescription or nonprescription medications without your approval. The instructions you leave may include the following:

- The symptoms of a bleed
- Your child’s limitations—what he can and cannot do
- Number(s) where you can be reached in case of an emergency
- Emergency contact names and phone numbers—your doctor and the local HTC

Some HTCs make day care center visits to educate the staff about hemophilia and other bleeding disorders. There are also publications available from HANDI, the information service of NHF, 1-800-42-HANDI.41

Things You May Want the Day Care or Preschool Staff to Be Aware of42:

- Any physical restrictions or limitations your child may have
- Your child’s medications and how they are used
- Symptoms of a bleed and how to treat it
- Names and phone numbers for emergency contacts, such as your doctor and the local HTC
- Where you can be reached during the day
FAMILY ISSUES IN THE EARLY CHILDHOOD YEARS
Psychosocial Implications of Hemophilia in Early Childhood

Two key issues that often arise early on with hemophilia are coping with the diagnosis and balancing vigilance and overprotectiveness.43*

- A diagnosis of hemophilia can cause emotions ranging from acceptance to denial, confusion, anger, guilt, and fear for the future. These feelings can complicate or contradict the joy of the baby’s arrival. The sooner these issues are confronted, the easier the adjustment will be—this is why the first years of interaction with the HTC are so important for families. For parents, the HTC should be a place where trust is built, and reliability and mutual education are assured.43*

- Parents may sometimes feel guilt at having passed on hemophilia to their child. They may be disappointed and angry that dreams for their child may not be fulfilled. Anxiety over access to treatment or cost of treatment and concern about venous access for the delivery of factor replacement may occur. Anxiety about family disruption and sibling rivalry over the attention spent on the child with hemophilia may develop along with fears about treatment and care.43*

Hemophilia affects not only the individual, but the whole family. Siblings should be included in counseling sessions and be given a basic understanding of hemophilia.43*

*As recommended by Cassis FRMY. Psychosocial Care for People With Hemophilia. Montréal, Québec: World Federation of Hemophilia; 2007.
Family Dynamics in the Hemophilia Home

Edward Kuebler, LCSW
Gulf States Hemophilia and Thrombophilia Center
Houston, Texas

Edward K, a member of the comprehensive care team at Gulf States Hemophilia and Thrombophilia Center in Houston, Texas, works with people to help them understand that hemophilia affects not just the individual, but the whole family. When a child is diagnosed with hemophilia, the family unit needs to re-evaluate how they will raise the child from this day forward. This thought often puts families into upheaval, and for this reason, Edward states, “It is very important that families immediately get involved with an HTC where they can find health professionals to help them assess their situation and identify approaches that will work for them. Many families simply don’t know what to do.”

At the HTC, they will have access to resources where all members of the comprehensive care team begin the process of education that will help families gain a better understanding of the bleeding disorder. Here they can meet other families with like situations who can share their experiences.
One of the areas Edward focuses on is helping parents identify when they are being overprotective of their child with hemophilia. He works with them to change this behavior by:

- Recognizing and talking about their fears
- Guiding them to understand that overprotection may hinder the child’s emotional, social, and physical development

Edward feels that it is important to watch for signs of difficult adjustment, such as parents rejecting or distancing themselves from the child, blaming the other (female) parent, feeling shame, or intense conflict in the family. “Parents don’t trust themselves to parent a child with hemophilia for the first year or two.” He works with families to achieve acceptance and to recognize that the dream they once had for their baby is now changed. Today, he helps them to move forward by learning to face each life stage as it arrives.

He feels that the Internet is a positive motivator in helping parents understand hemophilia because families are getting more information earlier. However, he does note that peer-to-peer communication is the most valuable resource for parents.
Tony R is the father of a 3-year-old boy, Eli, who has hemophilia B. Tony and his wife, Janya, believe very strongly that parents of a child with hemophilia must get involved in the hemophilia community in order to become knowledgeable about the disorder and to develop a strong support system for the family. He says he sees too many parents who are not involved and are not learning, and as a result, are having a difficult time managing their child with hemophilia B in their family unit.

Tony also believes it’s necessary that members of a family take part in the treatment regimen as often as possible. He and Janya, as well as their oldest daughter, asked the home care nurse to teach them how to infuse, and today they are all involved in Eli’s care.
When asked what he thought was the most important thing he could teach Eli about his hemophilia B now, Tony said, “Teach him to take care of himself by telling us when something hurts.” Tony and his wife worry about the future when Eli has to find a job and get his own insurance. Even though Eli is only 3 years old, Tony believes he should teach his young son to be his own advocate in his care. Eli also wears a MedicAlert® bracelet.

Tony and Janya have found that by getting involved in the hemophilia B community, they have been able to locate resources they never knew existed. For example, through involvement in the state hemophilia association, they found scholarship money available for their oldest daughter to attend college.
Jennifer M and her husband, Matthew, are the parents of four children: Kaitlyn, 14; Megan, 11; Emily, 5; and Nicholas, 3. Megan is a special needs child with Williams Syndrome and Nicholas has hemophilia B. There was no previous confirmed diagnosis of hemophilia in the family, although Jennifer’s brother died from an intracranial hemorrhage weeks after birth. A diagnosis of hemophilia was not expected when Nicholas was born until a heel-stick after birth produced oozing, a factor level of less than 1%, and a confirmative diagnosis of severe hemophilia B.

Nicholas was then treated with factor, and he remained in the hospital for 1 month after birth. His factor level improved, but he developed complications and will never be able to have a catheter. When he needs infusions now, his family takes him to the ER. Because of the complication, Nicholas is under the care of a cardiologist, as well as a hematologist.

Jennifer M and her family are extremely pleased with all of the resources available to them through the hemophilia B community. The family attends numerous events and conferences every year, and their older daughter, Kaitlyn, has become involved with other siblings of young children with hemophilia B. She recently attended “Advocacy Days” in Maryland with her parents, where she spoke with a local congressman about resources for children with hemophilia.
When we spoke with Jennifer, we asked her how she managed having a toddler with hemophilia and a young special needs child. Jennifer replied, “We haven’t stopped for hemophilia. We use all of the resources in the hemophilia B community, and as a family, we have made many friends.” She feels very strongly that every family with a child with hemophilia should get involved with an HTC as soon as possible and take advantage of the education and socialization available to the entire family.

When asked about concerns for the future, Jennifer said, “We worry about treatment for Nicholas as he gets older and the fact that he cannot have a port for proactive treatment. Right now he is on-demand only. We take lots of precautions in our home, and outside of the home as much as we can. For now, we focus on exercises for Nicholas.”

Nicholas will begin preschool in the fall, and Jennifer plans to hold an education session with the teachers and staff at the school. The family also plans to attend a camp with Nicholas in the near future.
Brad and Lisa S are the parents of 18-month-old twin boys, Eli and Max. Both boys have hemophilia B. Early on Lisa and Brad had the support of their family; however, they did not know a lot about the disorder even though Lisa’s father had hemophilia. As a result of this lack of knowledge, they decided to become educated immediately; so, they joined an HTC and their local hemophilia chapter. Through newly formed peer-to-peer relationships, a world opened up for them that began erasing some of the apprehension they initially had because of a lack of understanding of the disorder and fear of the future.

Brad believes that parents need to understand the process of a bleed and what can be done to help prevent injuries that inevitably happen in the toddler years. He says, “We’re getting stronger as we are going on. However, we are still nervous about injury now that the boys are walking.” Lisa did put extra cushioning into their clothing, and so far that is helping.
When asked about concerns for the future, Brad said, “We do have anxiety about what is ahead. We are concerned about how we will manage eventual treatments, both in terms of how the boys will respond and working out the logistics. We’ve made many trips to the ER for infusions, and it has been stressful at times. We also have concerns about keeping them safe while not being too overprotective, especially when they are outside of our home.” Brad and Lisa know how important socialization and exploration are to a child’s growth but admit that there are many stresses that go with this. While they have done everything possible to childproof their home, two active little boys can usually find something to get into.

Brad and Lisa both work and had difficulty making a decision to find day care. They did find a very capable nanny who has become very involved and knowledgeable in the treatment of Eli and Max.
BENEFIX® COAGULATION FACTOR IX (RECOMBINANT)
IMPORTANT PRODUCT INFORMATION
What Is BeneFİx® Coagulation Factor IX (Recombinant)?

BeneFİx is an injectable medicine that is used to help control and prevent bleeding in people with hemophilia B. Hemophilia B is also called congenital factor IX deficiency or Christmas disease.

BeneFİx is NOT used to treat hemophilia A.

Important Safety Information for BeneFİx

- BeneFİx is contraindicated in patients who have manifested life-threatening, immediate hypersensitivity reactions, including anaphylaxis, to the product or its components, including hamster protein.
- Call your health care provider right away if your bleeding is not controlled after using BeneFİx.
- Allergic reactions may occur with BeneFİx. Call your health care provider or get emergency treatment right away if you have any of the following symptoms: wheezing, difficulty breathing, chest tightness, your lips and gums turning blue, fast heartbeat, facial swelling, faintness, rash or hives.
- Your body can make antibodies, called “inhibitors,” which may interfere with the effectiveness of BeneFİx.
- If you have risk factors for developing blood clots, such as a venous catheter through which BeneFİx is given by continuous infusion, BeneFİx may increase the risk of abnormal blood clots. The safety and efficacy of BeneFİx administration by continuous infusion have not been established.
- Some common side effects of BeneFİx are nausea, injection site reaction, injection site pain, headache, dizziness and rash.

If you do not have prescription drug insurance and need help paying for BeneFİx, we may be able to help. Visit us at www.wyeth.com, or call us at 1-888-999-2349 for more information.

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.

Please see accompanying full Prescribing Information for BeneFİx.
We all realize parenting infants, toddlers, and preschoolers is no easy matter and a constant challenge under the best of circumstances. In a family in which a young child has hemophilia B, the stress, worry, and challenges are probably even greater. In many cases, the family is not prepared to manage a bleeding disorder and the changes it inevitably brings to the family unit. In speaking with many families with young children who have hemophilia B, there seems to be a common statement from most of them: “Get involved in the hemophilia B community.” Families benefit from the extensive resources in the community, including printed materials, family get-togethers, educational conferences, emotional support, and most of all, comprehensive hemophilia care at a local HTC. Within the hemophilia B community, families are certain to find others with similar situations who can offer guidance and support, as well as companionship for all members of the family during these early childhood years and for many years to come. The best protection and guidance we can offer our children is our complete involvement in their well-being.

Morris Green, MD, FAAP, Perry W. Lesh Professor of Pediatrics at Indiana University Medical Center said, “It has become increasingly clear that a child’s first 3 years of life largely determine his or her future developmental trajectory. To a large extent, these early years set the stage for later outcomes in personal health, emotional development, educational attainment, social competence, self-confidence, self-reliance, and positive human relationships. Parental investment in the coin of nurturance, care, love, and understanding during this formative age period brings both short- and long-term dividends.”

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On behalf of Pfizer Inc., The Coalition for Hemophilia B, Inc., and the B2B Consumer Advisory Board, we would like to extend our gratitude to the members of the hemophilia B community who contributed to this book. Your time, knowledge, and personal stories about life with hemophilia B are greatly appreciated.

Tony Roland
Jennifer Marlatt
Brad Schoenfeld

We would also like to thank the professionals involved with hemophilia care who shared their insights about hemophilia B.

Kim Spencer, MS, RN, CPNP
Thomas Truncale, DO, MPH, CIME
Edward Kuebler, LCSW
Resources

Arizona Hemophilia Association
North American Camping Conference of Hemophilia Organizations (NACCHO)
Phone: 1-888-754-7017
Web site: www.naccho.com

Canadian Hemophilia Society
Phone: 1-800-668-2686
Web site: www.hemophilia.ca

Centers for Disease Control and Prevention (CDC)
Hemophilia Treatment Centers
Web site: www.cdc.gov/ncbddd/hbd/htc_list.htm

The Coalition for Hemophilia B, Inc.
Phone: 1-212-520-8272
Web site: www.coalitionforhemophiliab.org

Hemophilia Federation of America (HFA)
Phone: 1-800-230-9797
Web site: www.hemophiliafed.org

Inalex Communications
Phone: 1-866-802-0304
Web site: www.inalex.com

LA Kelley Communications, Inc.
Phone: 1-800-249-7977
Web site: www.kelleycom.com

National Heart Lung and Blood Institute
Phone: 1-301-592-8573
Web site: www.nhlbi.nih.gov

National Hemophilia Foundation (NHF)
Phone: 1-800-424-2634 (42-HANDI)
Web site: www.hemophilia.org

Patient Services Inc. (PSI)
Phone: 1-800-366-7741
Web site: www.uneedpsi.org

World Federation of Hemophilia (WFH)
Phone: 1-514-875-7944
Web site: www.wfh.org
Pfizer Programs and Services

Pfizer Hemophilia Hotline
This hotline answers questions about Pfizer’s products and services: 1-888-999-2349.

Insurance-Coverage Program, Patient Assistance Program, Reimbursement-Information Line
We have many programs and services designed to help patients and families who are experiencing a gap in insurance coverage or are faced with the inability to obtain factor IX based on income.

Summer Camp Support
Pfizer sponsors camp information conferences, provides financial assistance for scholarships to camp, and donates emergency factor for campers. We know how important it is for children with hemophilia to make new friends and enjoy themselves with people who understand their disorder.

Soozie Courter “Sharing a Brighter Tomorrow” Hemophilia Scholarship Program
Pfizer provides scholarships to students with hemophilia A or hemophilia B who are high school seniors, have a graduate equivalency diploma (GED), or are currently enrolled in an accredited junior college, college (undergraduate or graduate), or vocational school. Awards are based on academics, recommendations, and a personal statement from the student. Visit www.hemophiliavillage.com to download an application.

Hemophiliavillage.com
The Pfizer-sponsored Web site, www.hemophiliavillage.com, provides information for the hemophilia community. Consumers and professionals alike can find product information and learn about programs and services.

World Federation of Hemophilia (WFH) Twinning Program
Pfizer Inc. is an exclusive sponsor of this program, which links hemophilia treatment centers (HTCs) in developed countries, such as the United States, with countries that have limited medical resources. The goal of the program is to help improve hemophilia care worldwide. For more information about this program, call 1-514-875-7944, or visit the Web site at www.wfh.org.
References


44. BeneFIX® Coagulation Factor IX (Recombinant) Prescribing Information, Wyeth Pharmaceuticals Inc.

This booklet was funded by Pfizer Inc.
and distributed in partnership with the The Coalition for Hemophilia B, Inc.
HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BeneFIX safely and effectively. See full prescribing information for BeneFIX.

BeneFIX [Coagulation Factor IX (Recombinant)]
For Intravenous Use, Lyophilized Powder for Reconstitution

Initial U.S. Approval: 1997

INDICATIONS AND USAGE

BeneFIX is an antihemophilic factor (recombinant) indicated for:

- Control and prevention of bleeding episodes in adult and pediatric patients with hemophilia B. (1.1)
- Peri-operative management in adult and pediatric patients with hemophilia B. (1.2)

Dosage and Administration

For Intravenous Use only

The initial estimated dose may be determined using the following formula:

Required units = body weight (kg) x desired factor IX increase (IU/dL or % of normal) x reciprocal of observed recovery (IU/kg per IU/dL)

Average Recovery: Adult and Pediatric (<15 years) Patients
In clinical studies with adult and pediatric (<15 years) patients, one IU of BeneFIX per kilogram of body weight increased the circulating activity of factor IX as follows:

- Adults: 0.8 ± 0.2 IU/dL [range 0.4 to 1.2 IU/dL]. (2.2)
- Pediatric: 0.7 ± 0.3 IU/dL [range 0.2 to 2.1 IU/dL]. (2.2)

Dosing of BeneFIX may differ from that of plasma-derived factor IX products.

Dosage and duration of treatment with BeneFIX depends on the severity of the factor IX deficiency, the location and extent of bleeding, and the patient’s clinical condition, age and recovery of factor IX. (2.1)

DOSE FORMS AND STRENGTHS

BeneFIX lyophilized powder is available as 250, 500, 1000, 2000, or 3000 IU in single-use vials. (3)

CONTRAINDICATIONS

BeneFIX is contraindicated in patients who have manifested life-threatening, immediate hypersensitivity reactions, including anaphylaxis, to the product or its components, including hamster protein. (4)

WARNINGS AND PRECAUTIONS

- Anaphylaxis and severe hypersensitivity reactions are possible. Should symptoms occur, treatment with the product should be discontinued, and emergency treatment should be sought. Patients may develop hypersensitivity to hamster (CHO) protein as BeneFIX contains trace amounts. (5.2)
- BeneFIX has been associated with the development of thromboembolic complications, including patients receiving continuous infusion through a central venous catheter. (5.3)
- Nephrotic syndrome has been reported following immune tolerance induction with factor IX products in hemophilia B patients with factor IX inhibitors and a history of allergic reactions to factor IX. (5.4)
- Development of activity-neutralizing antibodies has been detected in patients receiving factor IX-containing products. If expected plasma factor IX activity levels are not attained, or if patient presents with allergic reaction, or if bleeding is not controlled with an expected dose, an assay that measures factor IX inhibitor concentration should be performed. (5.5)

ADVERSE REACTIONS

The most common adverse reactions (incidence >5%) from clinical trials were nausea, injection site reaction, injection site pain, headache, dizziness and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Wyeth Pharmaceuticals Inc. at 1-800-934-5556 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

USE IN SPECIFIC POPULATIONS

Pregnancy: No human or animal data. Use only if clearly needed. (8.1)

Pediatric Use: On average, lower recovery has been observed in pediatric patients (<15 years). A dose adjustment may be needed. (12.3, 14)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 11/2011

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Control and Prevention of Bleeding Episodes in Hemophilia B

BeneFIX®, Coagulation Factor IX (Recombinant), is indicated for the control and prevention of bleeding episodes in adult and pediatric patients with hemophilia B (congenital factor IX deficiency or Christmas disease).

1.2 Peri-operative Management in Patients with Hemophilia B

BeneFIX, Coagulation Factor IX (Recombinant), is indicated for peri-operative management in adult and pediatric patients with hemophilia B.

BeneFIX, Coagulation Factor IX (Recombinant), is NOT indicated for:

a. treatment of other factor deficiencies (e.g., factors II, VII, VIII, and X),
b. treatment of hemophilia A patients with inhibitors to factor VIII,
c. reversal of coumarin-induced anticoagulation,
d. treatment of bleeding due to low levels of liver-dependent coagulation factors.

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations for Administration

For Intravenous Use after Reconstitution

- Treatment with BeneFIX, Coagulation Factor IX (Recombinant), should be initiated under the supervision of a physician experienced in the treatment of hemophilia B.
- Each vial of BeneFIX has the rFIX potency in the International Units (IU) stated on the vial.
- Dosage and duration of treatment for all factor IX products depend on the severity of the factor IX deficiency, the location and extent of bleeding, and the patient’s clinical condition, age and recovery of factor IX.

To ensure that the desired factor IX activity level has been achieved, precise monitoring using the factor IX activity assay is advised. Doses should be titrated using the factor IX activity, pharmacokinetic parameters, such as half-life and recovery, as well as taking the clinical situation into consideration in order to adjust the dose as appropriate.

Dosing of BeneFIX may differ from that of plasma-derived factor IX products [see Clinical Pharmacology (12)]. Subjects at the low end of the observed factor IX recovery may require upward dosage adjustment of BeneFIX to as much as two times (2X) the initial empirically calculated dose in order to achieve the intended rise in circulating factor IX activity.
The safety and efficacy of BeneFIX administration by continuous infusion have not been established [see Warnings and Precautions (5.3)].

2.2 Method of Calculating Initial Estimated Dose

The method of calculating the factor IX dose is shown in Table 1.

<table>
<thead>
<tr>
<th>number of factor IX IU required (IU)</th>
<th>body weight (kg)</th>
<th>desired factor IX increase (% or IU/dL)</th>
<th>reciprocal of observed recovery (IU/kg per IU/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

Table 1

Average Recovery Adult Patients in Clinical Trial

In adult PTPs, on average, one International Unit (IU) of BeneFIX per kilogram of body weight increased the circulating activity of factor IX by 0.8 ± 0.2 IU/dL (range 0.4 to 1.2 IU/dL). The method of dose estimation is illustrated in Table 2. If you use 0.8 IU/dL average increase of factor IX per IU/kg body weight administered, then:

<table>
<thead>
<tr>
<th>number of factor IX IU required (IU)</th>
<th>body weight (kg)</th>
<th>desired factor IX increase (% or IU/dL)</th>
<th>1.3 (IU/kg per IU/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

Table 2

Average Recovery Pediatric Patients (<15 years) in Clinical Trial

In pediatric patients, on average, one international unit of BeneFIX per kilogram of body weight increased the circulating activity of factor IX by 0.7 ± 0.3 IU/dL (range 0.2 to 2.1 IU/dL; median of 0.6 IU/dL per IU/kg). The method of dose estimation is illustrated in Table 3. If you use 0.7 IU/dL average increase of factor IX per IU/kg body weight administered, then:

<table>
<thead>
<tr>
<th>number of factor IX IU required (IU)</th>
<th>body weight (kg)</th>
<th>desired factor IX increase (% or IU/dL)</th>
<th>1.4 (IU/kg per IU/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

Table 3

Doses administered should be titrated to the patient’s clinical response. Patients may vary in their pharmacokinetic (e.g., half-life, in vivo recovery) and clinical responses to BeneFIX. Although the dose can be estimated by the calculations above, it is highly recommended that, whenever possible, appropriate laboratory tests, including serial factor IX activity assays, be performed.
2.3 Dosing Guide for Control and Prevention of Bleeding Episodes and Peri-operative Management

<table>
<thead>
<tr>
<th>Type of Hemorrhage</th>
<th>Circulating Factor IX Activity Required [% or (IU/dL)]</th>
<th>Dosing Interval [hours]</th>
<th>Duration of Therapy [days]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncomplicated hemarthroses, superficial muscle, or soft tissue</td>
<td>20-30</td>
<td>12-24</td>
<td>1-2</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intramuscle or soft tissue with dissection, mucous membranes, dental extractions, or hematuria</td>
<td>25-50</td>
<td>12-24</td>
<td>Treat until bleeding stops and healing begins, about 2 to 7 days</td>
</tr>
<tr>
<td><strong>Major</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharynx, retropharynx, retroperitoneum, CNS, surgery</td>
<td>50-100</td>
<td>12-24</td>
<td>7-10</td>
</tr>
</tbody>
</table>

Adapted from: Roberts and Eberst

2.4 Instructions for Use

BeneFIX is administered by intravenous (IV) infusion after reconstitution of the lyophilized powder with the supplied pre-filled diluent (0.234% sodium chloride solution) syringe.

Patients should follow the specific reconstitution and administration procedures provided by their physicians.

For instructions, patients should follow the recommendations in the FDA-Approved Patient Labeling [see Patient Counseling Information (17)].

Reconstitution, product administration, and handling of the administration set must be done with caution. Discard all equipment, including any reconstituted BeneFIX product, in an appropriate container. Place needles used for venipuncture in a sharps container after single use. Percutaneous puncture with a needle contaminated with blood from an infected patient can transmit infectious viruses including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs.

2.5 Preparation and Reconstitution

The procedures below are provided as general guidelines for the reconstitution and administration of BeneFIX.
Preparation

1. Always wash your hands before performing the following procedures.
2. Aseptic technique (meaning clean and germ-free) should be used during the reconstitution procedure.
3. Use all components in the reconstitution and administration of this product as soon as possible after opening their sterile containers to minimize unnecessary exposure to the atmosphere.
   Note: If you use more than one vial of BeneFIX per infusion, each vial should be reconstituted according to the following instructions. The diluent syringe should be removed leaving the vial adapter in place, and a separate large luer lock syringe may be used to draw back the reconstituted contents of each vial. Do not detach the diluent syringes or the large luer lock syringe until you are ready to attach the large luer lock syringe to the next vial adapter.

Reconstitution

1. If refrigerated allow the vial of lyophilized BeneFIX and the pre-filled diluent syringe to reach room temperature.
2. Remove the plastic flip-top cap from the BeneFIX vial to expose the central portions of the rubber stopper.

3. Wipe the top of the vial with the alcohol swab provided, or use another antiseptic solution, and allow to dry. After cleaning, do not touch the rubber stopper with your hand or allow it to touch any surface.
4. Peel back the cover from the clear plastic vial adapter package. **Do not remove the adapter from the package.**
5. Place the vial on a flat surface. While holding the adapter in the package, place the vial adapter over the vial and press down firmly on the package until the adapter spike penetrates the vial stopper.
6. Grasp the plunger rod as shown in the diagram. Avoid contact with the shaft of the plunger rod. Attach the threaded end of the plunger rod to the diluent syringe plunger by pushing and turning firmly.

7. Break off the tamper-resistant plastic-tip cap from the diluent syringe by snapping the perforation of the cap. Do not touch the inside of the cap or the syringe tip. The diluent syringe may need to be recapped (if not administering reconstituted BeneFIX immediately), so place the cap on its top on a clean surface in a spot where it would be least likely to become environmentally contaminated.

8. Lift the package away from the adapter and discard the package.

9. Place the vial on a flat surface. Connect the diluent syringe to the vial adapter by inserting the tip into the adapter opening while firmly pushing and turning the syringe clockwise until secured.
10. Slowly depress the plunger rod to inject all the diluent into the BeneFIX vial.

![Image of a syringe being used to inject diluent into a vial]

11. Without removing the syringe, gently swirl the contents of the vial until the powder is dissolved.

**Note:** The final solution should be inspected visually for particulate matter before administration. The solution should appear clear and colorless. If it is not, the solution should be discarded and a new kit should be used.

12. Invert the vial and slowly draw the solution into the syringe.

![Image of a syringe drawing solution from the vial]

13. Detach the syringe from the vial adapter by gently pulling and turning the syringe counter-clockwise. Discard the vial with the adapter attached.

**Note:** If the solution is not to be used immediately, the syringe cap should be carefully replaced. Do not touch the syringe tip or the inside of the cap.

**BeneFIX, when reconstituted, contains polysorbate-80, which is known to increase the rate of di-(2-ethylhexyl)phthalate (DEHP) extraction from polyvinyl chloride (PVC). This should be considered during the preparation and administration of BeneFIX, including storage time elapsed in a PVC container following reconstitution. It is important that the recommendations for dosage and administration be followed closely [see Dosage and Administration (2)].**

**Note:** The tubing of the infusion set included with this kit does not contain DEHP.

### 2.6 Administration (Intravenous Injection)

**For Intravenous Use only after Reconstitution**

BeneFIX is administered by intravenous (IV) infusion after reconstitution with the pre-filled diluent (0.234% sodium chloride solution) syringe.

- BeneFIX should be inspected for particulate matter and discoloration prior to administration, whenever solution and container permit.
The reconstituted solution may be stored at room temperature prior to administration, but BeneFIX should be administered within 3 hours. BeneFIX should be administered using the tubing provided in this kit, and the pre-filled diluent syringe provided, or a single sterile disposable plastic syringe. In addition, the solution should be withdrawn from the vial using the vial adapter.

A dose of BeneFIX may be administered over a period of several minutes. The rate of administration, however, should be adapted to the comfort level of each individual patient.

1. Attach the syringe to the luer end of the infusion set tubing provided.
2. Apply a tourniquet and prepare the injections site by wiping the skin well with an alcohol swab provided in the kit.

3. Perform venipuncture. Insert the needle on the infusion set tubing into the vein, and remove the tourniquet. The reconstituted BeneFIX product should be injected intravenously over several minutes. The rate of administration should be determined by the patient’s comfort level.

Reconstituted BeneFIX should not be administered in the same tubing or container with other medicinal products.

Agglutination of red blood cells in the tubing/syringe has been reported with the administration of BeneFIX. No adverse events have been reported in association with this observation. To minimize the possibility of agglutination, it is important to limit the amount of blood entering the tubing. Blood should not enter the syringe. If red blood cell agglutination is observed in the tubing or syringe, discard all material (tubing, syringe and BeneFIX solution) and resume administration with a new package.

Following completion of BeneFIX treatment, remove the infusion set and discard. Dispose of all unused solution, empty vial(s), and used needles and syringes in an appropriate container for throwing away waste that might hurt others if not handled properly.
The safety and efficacy of administration by continuous infusion have not been established [see Warnings and Precautions (5.3)].

3 DOSAGE FORMS AND STRENGTHS

BeneFIX is supplied as a white lyophilized powder in the following dosages:

- 250 IU
- 500 IU
- 1000 IU
- 2000 IU
- 3000 IU

4 CONTRAINDICATIONS

BeneFIX is contraindicated in patients who have manifested life-threatening, immediate hypersensitivity reactions, including anaphylaxis, to the product or its components, including hamster protein.

5 WARNINGS AND PRECAUTIONS

5.1 General

The clinical response to BeneFIX may vary. If bleeding is not controlled with the recommended dose, the plasma level of factor IX should be determined, and a sufficient dose of BeneFIX should be administered to achieve a satisfactory clinical response. If the patient’s plasma factor IX level fails to increase as expected or if bleeding is not controlled after the expected dose, the presence of an inhibitor (neutralizing antibodies) should be suspected, and appropriate testing performed [see Warnings and Precautions (5.6)].

5.2 Anaphylaxis and Severe Hypersensitivity Reactions

Allergic type hypersensitivity reactions, including anaphylaxis, have been reported with BeneFIX and have manifested as pruritus, rash, urticaria, hives, facial swelling, dizziness, hypotension, nausea, chest discomfort, cough, dyspnea, wheezing, flushing, discomfort (generalized) and fatigue. Frequently, these events have occurred in close temporal association with the development of factor IX inhibitors. Advise patients to discontinue use of the product and contact their physician and/or seek immediate emergency care.

BeneFIX contains trace amounts of hamster (CHO) proteins. Patients treated with this product may develop hypersensitivity to these non-human mammalian proteins.

5.3 Thromboembolic Complications

The safety and efficacy of BeneFIX administration by continuous infusion have not been established [see Dosage and Administration (2)]. There have been post-marketing reports of thrombotic events in patients receiving continuous-infusion BeneFIX through a central venous
catheter, including life-threatening superior vena cava (SVC) syndrome in critically ill neonates [see Adverse Reactions (6.2)].

5.4 Nephrotic Syndrome

Nephrotic syndrome has been reported following immune tolerance induction with factor IX products in hemophilia B patients with factor IX inhibitors and a history of allergic reactions to factor IX. The safety and efficacy of using BeneFIX for immune tolerance induction have not been established.

5.5 Neutralizing Antibodies (Immunogenicity)

Patients using BeneFIX should be monitored for the development of factor IX inhibitors by appropriate clinical observations and laboratory tests. Inhibitors have been reported following administration of BeneFIX [see Adverse Reactions (6.1)]. If expected plasma factor IX activity levels are not attained, or if bleeding is not controlled with an expected dose, an assay that measures factor IX inhibitor concentration should be performed.

Patients with factor IX inhibitors may be at an increased risk of anaphylaxis upon subsequent challenge with factor IX. Patients experiencing allergic reactions should be evaluated for the presence of an inhibitor. Patients should be observed closely for signs and symptoms of acute hypersensitivity reactions, particularly during the early phases of initial exposure to product. Because of the potential for allergic reactions with factor IX concentrates, the initial (approximately 10 - 20) administrations of factor IX should be performed under medical supervision where proper medical care for allergic reactions could be provided.

5.6 Monitoring Laboratory Tests

- Patients should be monitored for factor IX activity levels by the one-stage clotting assay to confirm that adequate factor IX levels have been achieved and maintained, when clinically indicated [see Dosage and Administration (2)].
- Patients should be monitored for the development of inhibitors if expected factor IX activity plasma levels are not attained, or if bleeding is not controlled with the recommended dose of BeneFIX. Assays used to determine if factor IX inhibitor is present should be titered in Bethesda Units (BUs).

6 ADVERSE REACTIONS

The most serious adverse reactions are systemic hypersensitivity reactions, including bronchospastic reactions and/or hypotension and anaphylaxis and the development of high-titer inhibitors necessitating alternative treatments to factor IX replacement therapy.

The most common adverse reactions observed in clinical trials (frequency > 5% of PTPs or PUPs) were headaches, dizziness, nausea, injections site reaction, injection site pain and skin-related hypersensitivity reactions (e.g., rash, hives).
6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

During uncontrolled open-label clinical studies with BeneFIX, Coagulation Factor IX (Recombinant), conducted in previously treated patients (PTPs), 113 adverse reactions with known or unknown relation to BeneFIX therapy were reported among 38.5% (25 of 65) of subjects (with some subjects reporting more than one event) who received a total of 7,573 infusions. These adverse reactions are summarized in Table 5.

Table 5: Adverse Reactions Reported for PTPs*

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Factor IX inhibition(^1)</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Blurred vision</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>4 (6.2%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Injection site reaction</td>
<td>5 (7.7%)</td>
</tr>
<tr>
<td></td>
<td>Injection site pain</td>
<td>4 (6.2%)</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
<td>2 (3.1%)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Cellulitis at IV site</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td></td>
<td>Phlebitis at IV site</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>7 (10.8%)</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>5 (7.7%)</td>
</tr>
<tr>
<td></td>
<td>Taste perversion (altered taste)</td>
<td>3 (4.6%)</td>
</tr>
<tr>
<td></td>
<td>Shaking</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td></td>
<td>Drowsiness</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Renal infarct(^2)</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dry cough</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td></td>
<td>Hypoxia</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td></td>
<td>Chest tightness</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>Skin and subcutaneous disorders</td>
<td>Rash</td>
<td>4 (6.2%)</td>
</tr>
<tr>
<td></td>
<td>Hives</td>
<td>2 (3.1%)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Flushing</td>
<td>2 (3.1%)</td>
</tr>
</tbody>
</table>

*Adverse reactions reported within 72 hours of an infusion of BeneFIX.
\(^1\) Low-titer transient inhibitor formation.
\(^2\) The renal infarct developed in a hepatitis C antibody-positive patient 12 days after a dose of BeneFIX for a bleeding episode. The relationship of the infarct to the prior administration of BeneFIX is uncertain.
In the 63 previously untreated patients (PUPs), who received a total of 5,538 infusions, 10 adverse reactions were reported among 9.5% of the patients (6 out of 63) having known or unknown relationship to BeneFIX. These events are summarized in Table 6.

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Factor IX inhibition(^1)</td>
<td>2 (3.2%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Injection site reaction</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Chills</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnea (respiratory distress)</td>
<td>2 (3.2%)</td>
</tr>
<tr>
<td>Skin and subcutaneous disorders</td>
<td>Hives</td>
<td>3 (4.8%)</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>1 (1.6%)</td>
</tr>
</tbody>
</table>

*Adverse reactions reported within 72 hours of an infusion of BeneFIX.

\(^1\) Two subjects developed high-titer inhibitor formation during treatment with BeneFIX.

For adverse reactions thought to be related to the administration of BeneFIX, the rate of infusion should be decreased or the infusion stopped.

### Immunogenicity

In clinical studies with 65 PTPs (defined as having more than 50 exposure days), a low-titer inhibitor was observed in one patient. The inhibitor was transient, the patient continued on study and had normal factor IX recovery pharmacokinetics at study completion (approximately 15 months after inhibitor detection).

In clinical studies with pediatric PUPs, inhibitor development was observed in 2 out of 63 patients (3.2%), both were high-titer (> 5 BU) inhibitors detected after 7 and 15 exposure days, respectively. Both patients were withdrawn from the study.

### 6.2 Post-marketing Experience

The following post-marketing adverse reactions have been reported for BeneFIX: inadequate factor IX recovery, inadequate therapeutic response, inhibitor development [see Clinical Pharmacology (12)], anaphylaxis [see Warnings and Precautions (5.2)], angioedema, dyspnea, hypotension, and thrombosis.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The safety and efficacy of BeneFIX administration by continuous infusion have not been established [see Warnings and Precautions (5.3)]. There have been post-marketing reports of thrombotic events, including life-threatening SVC syndrome in critically ill neonates, while receiving continuous-infusion BeneFIX through a central venous catheter. Cases of peripheral
thrombophlebitis and DVT have also been reported. In some, BeneFIX was administered via continuous infusion, which is not an approved method of administration [see Dosage and Administration (2)].

7 DRUG INTERACTIONS

None known.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction and lactation studies have not been conducted with BeneFIX, Coagulation Factor IX (Recombinant). It is not known whether BeneFIX can affect reproductive capacity or cause fetal harm when given to pregnant women. BeneFIX should be administered to pregnant women only if needed.

8.2 Labor and Delivery

There is no information available on the effect of factor IX replacement therapy on labor and delivery. Use only if needed.

8.3 Nursing Mothers

It is not known whether this drug is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised if BeneFIX is administered to nursing mothers.

Use only if needed.

8.4 Pediatric Use

Safety, efficacy, and pharmacokinetics of BeneFIX have been evaluated in previously treated (PTP) and previously untreated pediatric patients (PUP) [see Dosage and Administration (2), Clinical Pharmacology (12.3), Clinical Studies (14) and Adverse Reactions (6)]. On average, lower recovery has been observed in pediatric patients (<15 years). A dose adjustment may be needed [see Dosage and Administration (2) and Clinical Pharmacology (12.3)].

8.5 Geriatric Use

Clinical studies of BeneFIX did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Dose selection for an elderly patient should be individualized [see Dosage and Administration (2)].

10 OVERDOSAGE

No symptoms of overdose have been reported.
11 DESCRIPTION

BeneFIX, Coagulation Factor IX (Recombinant), is a purified protein produced by recombinant DNA. It has a primary amino acid sequence that is identical to the Ala\textsuperscript{148} allelic form of plasma-derived factor IX, and has structural and functional characteristics similar to those of endogenous factor IX. BeneFIX is produced by a genetically engineered Chinese hamster ovary (CHO) cell line that is extensively characterized. No human or animal proteins are added during the purification and formulation processes of BeneFIX.

BeneFIX is not derived from human blood and contains no preservatives, and the manufacture of BeneFIX includes no added animal or human components. The stored cell banks are free of human blood or plasma products. The CHO cell line secretes recombinant factor IX into a defined cell culture medium that does not contain any proteins derived from animal or human sources, and the recombinant factor IX is purified by a chromatography purification process that does not require a monoclonal antibody step. The process also includes a membrane nanofiltration step that has the ability to retain molecules with apparent molecular weights >70,000 Da (such as large proteins and viral particles). BeneFIX is a single component by SDS-polyacrylamide gel electrophoresis evaluation. The potency (in International Units, IU) is determined using an \textit{in vitro} one-stage clotting assay against the World Health Organization (WHO) International Standard for Factor IX concentrate. One International Unit is the amount of factor IX activity present in 1 mL of pooled, normal human plasma. The specific activity of BeneFIX is greater than or equal to 200 IU per milligram of protein.

BeneFIX is formulated as a sterile, nonpyrogenic, lyophilized powder preparation. BeneFIX is intended for intravenous (IV) injection. It is available in single-use vials containing the labeled amount of factor IX activity, expressed in IU. Each vial contains nominally 250, 500, 1000, 2000, or 3000 IU of Coagulation Factor IX (Recombinant). After reconstitution of the lyophilized drug product, the concentrations of excipients are 0.234% sodium chloride, 8 mM L-histidine, 0.8% sucrose, 208 mM glycine, 0.004% polysorbate 80. All dosage strengths yield a clear, colorless solution upon reconstitution.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

BeneFIX temporarily replaces the missing clotting factor IX that is needed for effective hemostasis.

12.2 Pharmacodynamics

The activated partial thromboplastin time (aPTT) is prolonged in people with hemophilia B. Treatment with factor IX concentrate may normalize the aPTT by temporarily replacing the factor IX. The administration of BeneFIX, Coagulation Factor IX (Recombinant), increases plasma levels of factor IX, and can temporarily correct the coagulation defect in these patients.
12.3 Pharmacokinetics

After single intravenous (IV) doses of 50 IU/kg of previously marketed BeneFIX, Coagulation Factor IX (Recombinant) [reconstituted with Sterile Water for Injection], in 37 previously treated adult patients (>15 years), each given as a 10-minute infusion, the mean increase from pre-infusion level in circulating factor IX activity was 0.8 ± 0.2 IU/dL per IU/kg infused (range 0.4 to 1.4 IU/dL per IU/kg) and the mean biologic half-life was 18.8 ± 5.4 hours (range 11 to 36 hours). In the original randomized, cross-over pharmacokinetic study in previously treated patients (PTPs), the \textit{in vivo} recovery using previously marketed BeneFIX was statistically significantly less (28% lower, \textit{p}<0.05) than the recovery using a highly purified plasma-derived factor IX product (pdFIX). A summary of pharmacokinetic data for BeneFIX and pdFIX are presented in Table 7.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BeneFIX, n = 11</th>
<th>pdFIX, n = 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{AUC}_\infty ) (IU·hr/dL)</td>
<td>548 ± 92</td>
<td>928 ± 191</td>
</tr>
<tr>
<td>( t_{1/2} ) (hr)</td>
<td>18.1 ± 5.1</td>
<td>17.7 ± 5.3</td>
</tr>
<tr>
<td>CL (mL/hr/kg)</td>
<td>8.62 ± 1.7</td>
<td>6.00 ± 1.4</td>
</tr>
<tr>
<td>K-value (IU/dL per IU/kg)</td>
<td>0.84 ± 0.30</td>
<td>1.17 ± 0.26</td>
</tr>
<tr>
<td>\textit{In vivo} Recovery (%)</td>
<td>37.8 ± 14.0</td>
<td>52.6 ± 12.4</td>
</tr>
</tbody>
</table>

Abbreviations: \( \text{AUC}_\infty \) = area under the plasma concentration-time curve from time zero to infinity; K-value = incremental recovery; \( t_{1/2} \) = plasma elimination half-life; CL = clearance; SD = standard deviation.

There was no significant difference in biological half-life. Structural differences of the BeneFIX molecule compared with pdFIX were shown to contribute to the lower recovery. In subsequent evaluations for up to 24 months, the pharmacokinetic parameters were similar to the initial results.

In a subsequent randomized, cross-over pharmacokinetic study, BeneFIX reconstituted in 0.234% sodium chloride diluent was shown to be pharmacokinetically equivalent to the previously marketed BeneFIX (reconstituted with Sterile Water for Injection) in 24 previously treated patients (≥12 years) at a dose of 75 IU/kg. In addition, pharmacokinetic parameters were followed up in 23 previously treated patients after repeated administration of BeneFIX for six months and found to be unchanged compared with those obtained at the initial evaluation. A summary of pharmacokinetic data are presented in Table 8:
Table 8: Pharmacokinetic Parameter Estimates for BeneFIX at Baseline (Cross-over phase) and Month 6 (Follow-up phase) in Previously Treated Patients with Hemophilia B

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parameters at Initial Visit (Cross-over phase), n = 24</th>
<th>Parameters at Month 6 (Follow-up phase), n = 23</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (IU/dL)</td>
<td>54.5 ± 15.0</td>
<td>57.3 ± 13.2</td>
</tr>
<tr>
<td>$\text{AUC}_{\infty}$ (IU·hr/dL)</td>
<td>940 ± 237</td>
<td>923 ± 205</td>
</tr>
<tr>
<td>$t_{1/2}$ (hr)</td>
<td>22.4 ± 5.3</td>
<td>23.8 ± 6.5</td>
</tr>
<tr>
<td>CL (mL/hr/kg)</td>
<td>8.47 ± 2.12</td>
<td>8.54 ± 2.04</td>
</tr>
<tr>
<td>K-value</td>
<td>0.73 ± 0.20</td>
<td>0.76 ± 0.18</td>
</tr>
<tr>
<td>$\text{In vivo}$ Recovery (%)</td>
<td>34.5 ± 9.3</td>
<td>36.8 ± 8.7</td>
</tr>
</tbody>
</table>

Abbreviations: AUC$_{\infty}$ = area under the plasma concentration-time curve from time zero to infinity; AUC$_{t}$ = area under the plasma concentration-time curve from zero to the last measurable concentration; $C_{\text{max}}$ = peak concentration; K-value = incremental recovery; $t_{1/2}$ = plasma elimination half-life; CL = clearance; SD = standard deviation.

**Pediatric Patients ($\leq$15 years)**

Nineteen (19) previously treated pediatric patients (range 4 to $\leq$15 years) underwent pharmacokinetic evaluations for up to 24 months. Fifty-eight previously untreated patients [PUPs] less than 15 years of age at baseline underwent at least one recovery assessment within 30 minutes post-infusion in the presence or absence of hemorrhage during the study. A total of 202 recovery assessments collected during the 60-month period from these 58 PUPs are combined with 19 recovery assessments from PTPs and were summarized by age group in Table 9. There was one recovery assessment in a neonate, which had a value of 0.46 IU/dL per IU/kg. The overall mean recovery and FIX elimination half-life values were 0.7 ± 0.3 IU/dL per IU/kg and 20.2 ± 4.0 hours, respectively.

Table 9: Summary of BeneFIX Pharmacokinetic Parameters in Pediatric Patients

<table>
<thead>
<tr>
<th>Age Group</th>
<th>n</th>
<th>K-value (IU/dL per IU/kg)</th>
<th>$t_{1/2}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants ($\geq$1 month to &lt;2 years)</td>
<td>33</td>
<td>0.7 ± 0.4 (0.2, 2.1)</td>
<td>ND</td>
</tr>
<tr>
<td>Children ($\geq$2 years to &lt;12 years)</td>
<td>61</td>
<td>0.7 ± 0.2 (0.2, 1.5)</td>
<td>19.8 ± 4.0 (14, 27)$^a$</td>
</tr>
<tr>
<td>Adolescents ($\geq$12 years to $\leq$15 years)</td>
<td>9</td>
<td>0.8 ± 0.3 (0.4, 1.4)</td>
<td>21.1 ± 4.5 (15, 28)$^b$</td>
</tr>
</tbody>
</table>

$^a$ n = 13
$^b$ n = 6

Data presented are mean ± standard deviation (min, max).

Abbreviations: ND = not determined; K-value = incremental recovery; $t_{1/2}$ = terminal phase elimination half-life.

Note: The columns are not mutually exclusive; individual patients may be listed under more than 1 age category.
Data from 57 PUP subjects who underwent repeat recovery testing for up to 60 months demonstrated that the average incremental FIX recovery was consistent over time, as shown in Figure 1.

Figure 1. Average Incremental rFIX Recovery over Time

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

BeneFIX, Coagulation Factor IX (Recombinant), has been shown to be nonmutagenic in the Ames assay and non-clastogenic in a chromosomal aberrations assay. No investigations on carcinogenesis or impairment of fertility have been conducted.

14 CLINICAL STUDIES

Efficacy of BeneFIX has been evaluated in clinical studies in which a total of 128 subjects received BeneFIX either for the treatment of bleeding episodes on an on-demand basis, for the prevention of bleeds (prophylaxis) or for management of hemostasis in the surgical setting (surgical prophylaxis).

Fifty-six PTPs and sixty-three PUPs were treated for bleeding episodes on an on-demand basis or for the prevention of bleeds (see Tables 9 and 10). The PTPs were followed over a median interval of 24 months (mean 23.4 ± 5.3 months) and for a median of 83.5. The PUPs were followed over a median interval of 37 months (mean 38.1 ± 16.4 months) and for a median of 89 exposure days.

Fifty-five PTPs and fifty-four PUPs received BeneFIX for the treatment of bleeding episodes (see Table 10). Bleeding episodes that were managed successfully included hemarthrosis and bleeding in soft tissue and muscle. Data concerning the severity of bleeding episodes were not
reported. In the PTPs, 88% of total infusions administrated for on-demand treatment were rated as an “excellent” or “good” response.

Table 10: Efficacy of BeneFIX for on-demand treatment of PTPs and PUPs

<table>
<thead>
<tr>
<th></th>
<th>Median dose: IU/kg (range)</th>
<th>Rate of bleeds resolved with 1 infusion</th>
<th>Response to 1st Infusion Rating&lt;sup&gt;c&lt;/sup&gt;</th>
<th>No Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTPs</td>
<td>N=55&lt;sup&gt;a&lt;/sup&gt; 42.8 (6.5 - 224.6)</td>
<td>81 %</td>
<td>Excellent/Good 90.9%</td>
<td>Moderate 7.1%</td>
</tr>
<tr>
<td>PUPs</td>
<td>N=54&lt;sup&gt;b&lt;/sup&gt; 62.7 (8.2 - 292)</td>
<td>75 %</td>
<td>Excellent/Good 94.1%</td>
<td>Moderate 2.9%</td>
</tr>
</tbody>
</table>

<sup>a</sup> One subject discontinued the study after one month of treatment due to bleeding episodes that were difficult to control; he did not have a detectable inhibitor.

<sup>b</sup> Three subjects were not successfully treated including one episode in a subject due to delayed time to infusion and insufficient dosing and in 2 subjects due to inhibitor formation.

<sup>c</sup> Response ratings not provided for 1.3% and 2% of 1st infusions for PTPs and PUPs, respectively.

A total of 20 PTPs were treated with BeneFIX for secondary prophylaxis (the regular administration of FIX replacement therapy to prevent bleeding in patients who may have already demonstrated clinical evidence of hemophilic arthropathy or joint disease) at some regular interval during the study with a mean of 2.0 infusions per week (see Table 11). Thirty-two PUPs were administered BeneFIX for routine (primary and secondary) prophylaxis (see Table 11). Twenty-four PUPs were administered BeneFIX at least twice weekly, and eight PUPs were administered BeneFIX once weekly. Seven PTPs experienced a total of 26 spontaneous bleeding episodes within 48 hours after an infusion. Six spontaneous bleeds within 48 hours after an infusion were reported in 5 PUPs. Prophylaxis therapy was rated as “excellent” or “effective” in 93% of PTPs receiving prophylaxis one to two times per week.
Table 11: Efficacy of Prophylaxis of BeneFIX in PTPs and PUPs

<table>
<thead>
<tr>
<th></th>
<th>Total exposure (infusions)</th>
<th>Duration of prophylaxis (months) (mean ± SD)</th>
<th>Dose IU/kg (mean ± SD)</th>
<th>Spontaneous bleeds within 48 hrs of infusion</th>
<th>Response rating&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Excellent</td>
</tr>
<tr>
<td>PTPs</td>
<td>20</td>
<td>18.2 ± 8.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>40.3 ± 15.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>28</td>
<td>56.0%</td>
</tr>
<tr>
<td>PUPs</td>
<td>32</td>
<td>14.4 ± 8.1</td>
<td>73.3 ± 33.1</td>
<td>6</td>
<td>91.3%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Response ratings provided at approximately 3-month intervals. In total, 116 and 172 assessments reported for PTPs and PUPs, respectively. Response ratings not provided for 2.6% and 0.6% of intervals for PTPs and PUPs, respectively.

<sup>b</sup> N = 19

Management of hemostasis was evaluated in the surgical setting in both PTPs and PUPs (see Table 12). Thirty-six surgical procedures have been performed in 28 PTPs with 23 major surgical procedures performed (including 6 complicated dental extractions). Thirty surgical procedures have been performed in 23 PUPs. Twenty-eight of these procedures were considered minor. Hemostasis was maintained throughout the surgical period; however, one PTP subject required evacuation of a surgical wound-site hematoma, and another PTP subject who received BeneFIX after a tooth extraction required further surgical intervention due to oozing at the extraction site. There was no clinical evidence of thrombotic complications in any of the subjects.

Among the PTP surgery subjects, the median increase in circulating factor IX activity was 0.7 IU/dL per IU/kg infused (range 0.3 – 1.2 IU/dL; mean 0.8 ± 0.2 IU/dL per IU/kg). The median elimination half-life for the PTP surgery subjects was 19.4 hours (range 10 – 37 hours; mean 21.3 ± 8.1 hours).
### Table 12: Efficacy of BeneFIX for Surgical Procedures in PTPs and PUPs

<table>
<thead>
<tr>
<th>Surgery Type</th>
<th>Number of Procedures (Number of Subjects)</th>
<th>Response</th>
<th>Excellent/Good</th>
<th>Moderate</th>
<th>No Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Previously Treated Patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ankle surgery</td>
<td>2 (2)</td>
<td></td>
<td>2 (100%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hip prosthesis implant (right)</td>
<td>1 (1)</td>
<td></td>
<td>1 (100%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Knee arthroplasty (2 bilateral, 1 right)</td>
<td>3 (3)</td>
<td></td>
<td>3 (100%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Knee arthroscopic synovectomy</td>
<td>2 (2)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>1 (50%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Liver transplantation (orthotopic)</td>
<td>1 (1)</td>
<td></td>
<td>1 (100%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>1 (1)</td>
<td></td>
<td>1 (100%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>External fixation device removal (wrist)</td>
<td>1 (1)</td>
<td></td>
<td>1 (100%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hernia repair</td>
<td>3 (2)</td>
<td></td>
<td>3 (100%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Subacromial decompression (left)</td>
<td>1 (1)</td>
<td></td>
<td>1 (100%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Calf debridement, dental extraction&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 (1)</td>
<td>1 (100%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lymph node removal, dental extraction&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 (1)</td>
<td>1 (100%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Left heel cord lengthening</td>
<td>1 (1)</td>
<td></td>
<td>1 (100%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dental procedures&lt;sup&gt;c&lt;/sup&gt;</td>
<td>12 (11)</td>
<td></td>
<td>11 (92%)</td>
<td>1 (8%)</td>
<td>-</td>
</tr>
<tr>
<td>Minor procedures</td>
<td>6 (6)</td>
<td></td>
<td>6 (100%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Previously Untreated Patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hernia repair</td>
<td>2 (2)</td>
<td></td>
<td>2 (100%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Minor procedures</td>
<td>28 (21)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>27 (96%)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> Response assessment not provided for 1 procedure.

<sup>b</sup> Includes pulse and continuous-infusion regimens; CI counted as 1 procedure in this summary.

<sup>c</sup> Includes complicated extractions (6), clearance, and fillings.

Nine of the major surgical procedures were performed in 8 PUPs using a continuous-infusion regimen. Five of the surgical procedures were performed in PUPs using a continuous-infusion regimen over 3 to 5 days. Although circulating factor IX levels targeted to restore and maintain hemostasis were achieved with both pulse replacement and continuous infusion regimens, clinical trial experience with continuous infusion of BeneFIX for surgical prophylaxis in hemophilia B has been too limited to establish the safety and clinical efficacy of administration of the product by continuous infusion.
All subjects participating in the PTP, PUP and surgery studies were monitored for clinical evidence of thrombosis [see Warnings and Precautions (5.3)]. No thrombotic complications were reported in PUPs or surgery subjects. One PTP subject experienced a renal infarct 12 days after a dose of BeneFIX for a bleeding episode; the relationship of the infarct to the prior administration of BeneFIX is uncertain. Laboratory studies of thrombogenicity (fibrinopeptide A and prothrombin fragment 1 + 2) were obtained in 41 PTPs and 7 surgery subjects prior to infusion and up to 24 hours following infusion. The results of these studies were inconclusive. Out of 29 PTP subjects noted to have elevated fibrinopeptide A levels post-infusion of BeneFIX, 22 also had elevated levels at baseline. Surgery subjects showed no evidence of significant increase in coagulation activation.

15 REFERENCES


16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

BeneFIX, Coagulation Factor IX (Recombinant), is supplied in kits that include single-use vials which contain nominally 250, 500, 1000, 2000, or 3000 IU per vial with sterile pre-filled diluent syringe, vial adapter reconstitution device, sterile infusion set, and two (2) alcohol swabs, one bandage, and one gauze pad. Actual factor IX activity in IU is stated on the label of each vial.

Product labeled “Room Temperature Storage”. Store at 2 to 30°C (36 to 86°F).

<table>
<thead>
<tr>
<th>IU</th>
<th>NDC number</th>
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<tbody>
<tr>
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</tr>
<tr>
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<tr>
<td>3000</td>
<td>58394-637-03</td>
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</table>

Product labeled for refrigeration. Store at 2 to 8°C (36 to 46°F).

<table>
<thead>
<tr>
<th>IU</th>
<th>NDC number</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
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<tr>
<td>500</td>
<td>58394-002-06</td>
</tr>
<tr>
<td>1000</td>
<td>58394-001-06</td>
</tr>
<tr>
<td>2000</td>
<td>58394-008-02</td>
</tr>
</tbody>
</table>
16.2 Storage and Handling

Product kit as packaged for sale: BeneFIX, Coagulation Factor IX (Recombinant), can be stored at room temperature or under refrigeration, at a temperature of 2 to 30°C (36 to 86°F). Do not use BeneFIX after the expiration date on the label. Different storage conditions are described below:

**Product labeled for Room Temperature Storage**

| Store at 2 to 30°C (36 to 86°F). | If the product kit is labeled for room temperature storage, it can be stored at room temperature (not to exceed 30°C or 86°F) or under refrigeration (2 to 8°C or 36 to 46°F). |

**Product labeled for Refrigerated Storage**

| Continuous refrigeration [2 to 8°C (36 to 46°F)] | If the product kit labeled for refrigerated storage has been continuously refrigerated at 2 to 8°C (36 to 46°F), the labeled expiration date on the package is still applicable and the product kit should be stored as labeled on the carton. Prior to the expiration date, the product kit may be stored at room temperature, not to exceed 30°C (86°F), for up to 6 months. If the product kit labeled for refrigerated storage has been removed from refrigeration and stored at room temperature (not to exceed 30°C or 86°F)*, the expiration period should be up to 6 months from the date of removal from refrigeration. Do not use the product once this six month period has elapsed even if the expiration date on the carton has not been exceeded. |

*If you have removed the product kit labeled for refrigerated storage from refrigeration as a result of our April 2011 communication on the “Daily Med”, and have not recorded the date of removal from refrigeration, the assigned expiration date (printed on the end flap of the product carton) **must be reduced by 12 months**.

Do not freeze to prevent damage to the diluent syringe.

**Product after reconstitution:** The product does not contain a preservative and should be used within 3 hours.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling

Advise patients to report any adverse reactions or problems following BeneFIX administration to their physician or healthcare provider.

- Allergic-type hypersensitivity reactions are possible. Inform patients of the early signs of hypersensitivity reactions [including hives (rash with itching), generalized urticaria,
tightness of the chest, wheezing, hypotension] and anaphylaxis. Advise patients to discontinue use of the product and contact their physicians if these symptoms occur.

- Advise patients to contact their physician or treatment facility for further treatment and/or assessment if they experience a lack of a clinical response to factor IX replacement therapy, as in some cases this may be a manifestation of an inhibitor.

FDA-Approved Patient Labeling

BeneFIX® / BEN-uh-fiks/

[Coagulation Factor IX (Recombinant)]

Please read this Patient Leaflet carefully before using BeneFIX and each time you get a refill. There may be new information. This Patient Leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

What is BeneFIX?

BeneFIX is an injectable medicine that is used to help control and prevent bleeding in people with hemophilia B. Hemophilia B is also called congenital factor IX deficiency or Christmas disease.

BeneFIX is NOT used to treat hemophilia A.

What should I tell my doctor before using BeneFIX?

Tell your doctor 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 medicines.

Tell your doctor about all of your medical conditions, including if you:

- are pregnant or planning to become pregnant. It is not known if BeneFIX may harm your unborn baby.
- are breastfeeding. It is not known if BeneFIX passes into the milk and if it can harm your baby.

How should I infuse BeneFIX?

The initial administrations of BeneFIX should be administered under proper medical supervision, where proper medical care for severe allergic reactions could be provided.

See the step-by-step instructions for infusing BeneFIX at the end of this leaflet. You should always follow the specific instructions given by your doctor. The steps listed below are general guidelines for using BeneFIX. If you are unsure of the procedures, please call your doctor or pharmacist before using.
Call your doctor right away if bleeding is not controlled after using BeneFIX.

Your doctor will prescribe the dose that you should take.

Your doctor may need to test your blood from time to time.

BeneFIX should not be administered by continuous infusion.

**What if I take too much BeneFIX?**

Call your doctor if you take too much BeneFIX.

**What are the possible side effects of BeneFIX?**

Allergic reactions may occur with BeneFIX. Call your doctor or get emergency treatment right away if you have any of the following symptoms:

- **wheezing**
- **difficulty breathing**
- **chest tightness**
- **turning blue (look at lips and gums)**
- **fast heartbeat**
- **swelling of the face**
- **faintness**
- **rash**
- **hives**

Your body can also make antibodies, called “inhibitors,” against BeneFIX, which may stop BeneFIX from working properly.

Some common side effects of BeneFIX are nausea, injection site reaction, injection site pain, headache, dizziness and rash.

BeneFIX may increase the risk of thromboembolism (abnormal blood clots) in your body if you have risk factors for developing blood clots, including an indwelling venous catheter through which BeneFIX is given by continuous infusion. There have been reports of severe blood clotting events, including life-threatening blood clots in critically ill neonates, while receiving continuous-infusion BeneFIX through a central venous catheter. The safety and efficacy of BeneFIX administration by continuous infusion have not been established.

These are not all the possible side effects of BeneFIX.
Tell your doctor about any side effect that bothers you or that does not go away.

**How should I store BeneFIX?**

**DO NOT FREEZE** BeneFIX kit.

BeneFIX kit can be stored at room temperature (below 86°F) or under refrigeration.

Throw away any unused BeneFIX and diluent after the expiration date indicated on the label.

Different storage conditions are described below.

**Product labeled for Room Temperature Storage**

| Store at 2 to 30°C (36 to 86°F). | If you have the product kit labeled for room temperature storage, it can be stored at room temperature (below 30°C or 86°F) or in the refrigerator (2 to 8°C or 36 to 46°F). |

**Product labeled for Refrigerated Storage**

| Continuous refrigeration [2 to 8°C (36 to 46°F)] | If you have the product kit labeled for storage in the refrigerator (2 to 8°C or 36 to 46°F) and you have not taken the kit out of the refrigerator, then the expiration date printed on the package still applies. You can store the product at room temperature (below 30°C or 86°F) for up to 6 months or until it has reached its expiration date, whichever comes first. If you have taken the product kit labeled for storage in the refrigerator out of the refrigerator and stored it at room temperature (below 30°C or 86°F), then use the product within 6 months from the time you took the product out of the refrigerator or until it has reached its expiration date, whichever comes first. If you cannot remember when you took the product out of the refrigerator, then subtract one year (12 months) from the date that is printed on the end flap of the carton package. The date you get is your new expiration date. Throw away any product that has gone over the new expiration date. |

Freezing should be avoided to prevent damage to the pre-filled diluent syringe.

BeneFIX does not contain a preservative. After reconstituting BeneFIX, you can store it at room temperature for up to 3 hours. If you have not used it in 3 hours, throw it away.

Do not use BeneFIX if the reconstituted solution is not clear and colorless.
What else should I know about BeneFIX?

Medicines are sometimes prescribed for purposes other than those listed here. Do not use BeneFIX for a condition for which it was not prescribed. Do not share BeneFIX with other people, even if they have the same symptoms that you have.

This Patient Leaflet summarizes the most important information about BeneFIX. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about BeneFIX that was written for healthcare professionals.

Instructions for Using BeneFIX

BeneFIX is supplied as a powder. Before it can be infused in your vein (intravenous injection), you must reconstitute the powder by mixing it with the liquid diluent supplied. The liquid diluent is 0.234% sodium chloride. BeneFIX should be reconstituted and infused using the infusion set, diluent, syringe, and adapter provided in this kit, and by following the directions below.

RECONSTITUTION

Always wash your hands before performing the following steps. Try to keep everything clean and germ-free while you are reconstituting BeneFIX. Once you open the vials, you should finish reconstituting BeneFIX as soon as possible. This will help keep the infusion set materials germ-free.

Note: If you use more than one vial of BeneFIX per infusion, reconstitute each vial according to steps 1 through 13.

1. If refrigerated, let the vial of BeneFIX and the pre-filled diluent syringe reach room temperature.
2. Remove the plastic flip-top cap from the BeneFIX vial to show the center part of the rubber stopper.

3. Wipe the top of the vial with the alcohol swab provided, or use another antiseptic solution, and allow to dry. After cleaning, do not touch the rubber stopper with your hand or allow it to touch any surface.
4. Peel back the cover from the clear plastic vial adapter package. Do not remove the adapter from the package.
5. Place the vial on a flat surface. While holding the adapter in the package, place the vial adapter over the vial. Press down firmly on the package until the adapter snaps into place on top of the vial, with the adapter spike penetrating the vial stopper.

6. Grasp the plunger rod as shown in the picture below. Do not touch the shaft of the plunger rod. Attach the threaded end of the plunger rod to the diluent syringe plunger by pushing and turning firmly.

7. Break off the tamper-resistant, plastic-tip cap from the diluent syringe by snapping the perforation of the cap. Do not touch the inside of the cap or the syringe tip. The diluent syringe may need to be recapped (if reconstituted BeneFIX is not used immediately), so place the cap on its tip on a clean surface in a spot where it will stay clean.

8. Lift the package away from the adapter and discard the package.
9. Place the vial on a flat surface. Connect the diluent syringe to the vial adapter by inserting the tip of the syringe into the adapter opening while firmly pushing and turning the syringe clockwise until the connection is secured.

10. Slowly push the plunger rod to inject all the diluent into the BeneFIX vial.

11. With the syringe still connected to the adapter, **gently** swirl the contents of the vial until the powder is dissolved.
   Look at the final solution before infusing it. The solution should be clear to colorless. If it is not, throw away the solution and use a new kit.

12. Make sure the syringe plunger rod is still fully pressed down, then turn over the vial. Slowly pull the solution into the syringe. Turn the syringe upward again and remove any air bubbles by gently tapping the syringe with your finger and slowly pushing air out of the syringe.
   If you reconstituted more than one vial of BeneFIX, remove the diluent syringe from the vial adapter and leave the vial adapter attached to the vial. Quickly attach a separate large luer lock syringe and pull the reconstituted solution as instructed above. Repeat this procedure with each vial in turn. Do not detach the diluent syringes or the large luer lock syringe until you are ready to attach the large luer lock syringe to the next vial adapter.
13. Remove the syringe from the vial adapter by gently pulling and turning the syringe counter-clockwise. Throw away the vial with the adapter attached.

If you are not using the solution right away, you should carefully replace the syringe cap. Do not touch the syringe tip or the inside of the cap.

BeneFIX should be infused within 3 hours after reconstitution. The reconstituted solution may be stored at room temperature prior to infusion.

INFUSION (Intravenous Injection)

Continuous infusion is **not** an approved way to administer BeneFIX.

Your doctor or healthcare professional should teach you how to infuse BeneFIX. Once you learn how to self-infuse, you can follow the instructions in this insert.

1. Attach the syringe to the luer end of the provided infusion set tubing.
2. Apply a tourniquet and prepare the injection site by wiping the skin well with an alcohol swab provided in the kit.

3. Insert the butterfly needle of the infusion set tubing into your vein as instructed by your doctor or healthcare provider. Remove the tourniquet. Infuse the reconstituted BeneFIX product over several minutes. Your comfort level should determine the rate of infusion.

Clumping of red blood cells in the tubing/syringe has been reported with the administration of BeneFIX. No adverse events have been reported in association with this observation. To minimize the possibility of clumping it is important to limit the amount of blood entering the tubing. Blood should not enter the syringe.

Note: If red blood cell clumping is observed in the tubing or syringe, discard all material (tubing, syringe and BeneFIX solution) and continue administration with a new package.
4. After infusing BeneFIX, remove the infusion set and discard. The amount of drug product left in the infusion set will not affect your treatment. Dispose of all unused solution, the empty vial(s), and the used needles and syringes in an appropriate container used for throwing away waste that might hurt others if not handled properly.

It is a good idea to record the lot number from the BeneFIX vial label every time you use BeneFIX. You can use the peel-off label found on the vial to record the lot number.

If you have any questions or concerns about BeneFIX, ask your doctor or healthcare provider.