Important Information for Patients with Hemophilia B (Factor IX Deficiency) without Inhibitors
New Treatment Available: Hemgenix® (Etranacogene Dezaparvovec)

Adeno-Associated Virus Vector-Based Gene Therapy

On November 22nd, 2022, the FDA approved Hemgenix®. This is the first gene therapy drug to treat adults with Hemophilia B (Factor IX deficiency) without inhibitors. To take Hemgenix® you must also meet one of these conditions:

- Currently use Factor IX prophylaxis therapy, or
- Have current or historical life-threatening bleeding, or
- Have had repeated, serious spontaneous bleeding episodes.

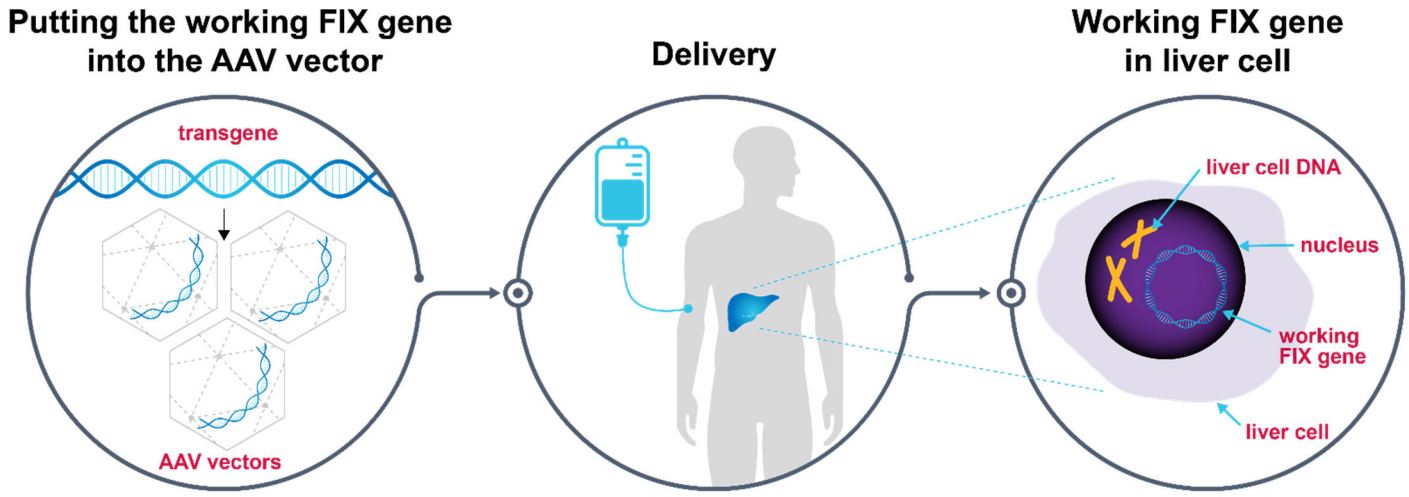
What does Hemgenix® do?

Hemgenix® may help you keep a steady level of FIX (a clotting factor) in your blood. Many people who take Hemgenix® no longer need to use other factor replacements. However, some people will still have low levels of FIX and still need factor infusions.

How does Hemgenix® work?

When you have Hemophilia B, your gene that makes FIX does not work properly. Hemgenix® uses a virus that is not dangerous to humans to deliver a working copy of the FIX gene to your liver. This gene lets your liver cells make normal FIX and release it into your blood.

- A virus is used as a vector to bring the working copy of the FIX gene into the liver. Think of a vector as a suitcase carrying the gene. This virus is not dangerous to humans. The vector is called an adeno-associated virus vector, or AAV vector.
- The working FIX gene is put into liver cells. It does not become part of your genes. You can't pass this normal FIX gene down to your children.
- The working gene will start making FIX for you.



How has Hemgenix® been studied?

Two clinical trials have studied Hemgenix® to see how safe it is and how well it works. Both studies followed adult males with moderately severe or severe Hemophilia B who received a single dose of Hemgenix®. The study participants were then followed for 5 years.

How do you take Hemgenix®?

Hemgenix® is given as a one-time infusion into a vein with a needle. Your dose is based on your weight. You must get the infusion at a specialized center, such as IHTC. It's usually given over several hours. You will need to be watched at the center for 3 hours after the infusion.

What are the possible benefits of Hemgenix®?

Many people who take Hemgenix® have increased FIX levels. People with moderately severe to severe Hemophilia B usually have FIX levels of 5% or lower before taking Hemgenix®. Studies have shown an average FIX activity level of 41.5% one year after taking Hemgenix®, and 36.7% two years after taking Hemgenix®. People who are treated with Hemgenix® may need fewer or no additional factor infusions. Their bodies are making more FIX, so they have fewer bleeding symptoms from Hemophilia B.

What are the possible disadvantages of Hemgenix®?

Hemgenix® is given as a one-time infusion, but people who take Hemgenix® will need frequent clinic visits and close monitoring for years after treatment. Possible serious side effects include:

- Liver damage. Some people may need to take steroids for a few months to reverse this damage.
- Becoming immune (or resistant) to the gene therapy vector. This may prevent use of another gene therapy if this treatment fails.
- Possible increased risk of cancer.

The most common side effects of Hemgenix are:

- Facial flushing (face getting red and hot)
- Feeling cold
- Shivering
- Rise in blood pressure
- Stomach pain
- Tight feeling in throat
- Itching
- Headache
- Feeling dizzy
- Tight feeling in chest

In clinical trials, 24 out of 54 (44%) people had abnormal liver function tests, and 9 out of 54 (17%) people needed treatment with steroids as a result. On average, these 9 people needed steroid treatment for 80 days.

The actual level of FIX activity after taking Hemgenix® may be different for each person. Not everyone will have improvements up to the level that was shown in the studies.

Hemgenix® uses a virus as a vector to transmit the working FIX gene to your liver. Even though this virus and gene doesn't cause an illness in humans, it is present in your blood and other body fluids after you take Hemgenix®. Because of this, people who receive Hemgenix® are not able to donate blood, organs, tissues, or cells for transplant. This is to avoid passing the virus on to other people.

The IHTC team is working to understand how insurance will cover gene therapy for our patients. We are happy to talk about this with you.

Who can take Hemgenix®?

- People who are over 18 with Hemophilia B who do not have an inhibitor. You must also meet one of these conditions:
  - Use FIX prophylaxis therapy
  - Have had repeated, life-threatening bleeding
  - Have had repeated, serious bleeding episodes with no known cause

You cannot take Hemgenix® if you:

- Are under age 18
- Have liver problems
- Have an inhibitor against FIX
- Cannot take steroids (some patients needed steroids for liver irritation)
- Have been exposed to the virus vector in the past and have immunity to the virus vector. You will need to talk about this with your doctor. Some people with a past immune response to the virus vector still had improved FIX levels depending on the level of immunity.
- Cannot come to frequent follow up visits and lab draws at your hemophilia treatment center. You might have to come for more frequent visits and labs if you have side effects. You will need to talk about this with your doctor before starting treatment.

Almost all the people in the trial with past exposure and immunity to the virus vector still responded to this gene therapy. One person with a very strong immune response did not have an increase in FIX activity with this gene therapy. Right now, we aren't sure how people with a strong immune response to the virus vector will respond to treatment. If you test positive for past immunity to the vector, you should talk about this with your doctor.

Will Hemgenix® Cure My Hemophilia?

While studies showed a significant improvement in FIX activity, most people went from having a severe or moderately severe FIX deficiency to having a mild deficiency. This means they still had mild Hemophilia B and may still need some treatment at times. Your FIX activity levels may also go down over time. After being treated with Hemgenix®, it is very important to continue close follow up with your hemophilia treatment center. It is important to understand that you will still pass on the gene for Hemophilia B to your daughters, even if they are born after your treatment with Hemgenix®.

This is a short explanation of gene therapy. If you have questions or are interested in talking more about if gene therapy with Hemgenix® is right for you, please contact your IHTC doctor, Dr. Amy Shapiro, or Jennifer Maahs, PNP at 1.877.256.8837.

Manufacturer	UniQure/CSL Behring
Studies performed	HEMGENIX® was evaluated in a prospective, open-label, single-dose, single-arm, multi-national study, HOPE-B (N = 54). The study enrolled adult male subjects aged 19 to 75 years, with severe or moderately severe Hemophilia B, who received a single intravenous dose of 2 × 1013 gc/kg body weight of HEMGENIX® and entered a follow-up period of 5 years. The study is on-going. Two subjects were not able to stop routine prophylaxis after HEMGENIX® treatment. One additional subject required prophylaxis from Days 396-534 [approximately 20 weeks]. In December 2020, the U.S. Food and Drug Administration (FDA) had put the AMT-061 program on hold after one subject developed hepatocellular carcinoma. A comprehensive investigation, conducted by an independent laboratory and reviewed by leading external experts, concluded that the adeno-associated virus (AAV) vector used in the gene therapy did not lead to that case of liver cell cancer. One subject with numerous cardiovascular and urologic risk factors, aged 75 years at screening, died of urosepsis and cardiogenic shock at Month 15 post-dose (at age 77 years) unrelated to treatment. Another subject received around 10% of the intended dose of HEMGENIX® due to an infusion-related hypersensitivity reaction.; this subject was not able to stop prophylaxis with FIX infusions.
Pre-infusion testing	Check if participant fulfills inclusion and exclusion criteria: liver health (viral infections, liver ultrasound, liver function), vector-related antibodies, factor activity, FIX activity and inhibitor
Post-infusion monitoring (Approximate)	First 6 months: 1-3 times per week 6-12 months: Monthly 12-24 months: 1-3 months >2 years: every three months
Risks with gene transfer	Infusion reactions, liver toxicity Possible: antibody to transgene product, tumorigenesis, central nervous system toxicity, severe liver toxicity
Risks: immunosuppression	**Drug specific**: elevated blood pressure, weight gain, high glucose levels, acne, headache, irritability, sleep disturbance, impaired wound healing, gastrointestinal toxicity, electrolyte/kidney abnormalities, blood abnormalities **Related to steroids used for treatment of liver toxicity**: infections, tissue inflammation, cancer risk, high glucose levels
Risks with transgene expression	Some patients may lose FIX activity over time (loss of transgene expression) or develop antibodies against the transgene.
Cost and availability	Gene therapy is an expensive treatment, issues related to insurance coverage are being evaluated. Please call with questions.

References:

1. Nathwani AC, McIntosh J, Sheridan R. Liver Gene Therapy. *Human gene therapy.* 2022;33(17-18):879-888.
2. FDA gov. https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapy-treat-adults-hemophilia-b. Accessed 20/12/2022.
3. Shah J, Kim H, Sivamurthy K, Monahan PE, Fries M. Comprehensive analysis and prediction of long-term durability of factor IX activity following etranacogene dezaparvovec gene therapy in the treatment of hemophilia B. *Current medical research and opinion.* 2022:1-11.
4. Chowdary P, Shapiro S, Makris M, et al. Phase 1-2 Trial of AAVS3 Gene Therapy in Patients with Hemophilia B. *N Engl J Med.* 2022;387(3):237-247.
5. Pipe SW, Recht M, Key NS, et al. Efficacy and safety of etranacogene dezaparvovec in adults with severe or moderate-severe hemophilia B: First data from the Phase 3 HOPE-B gene therapy trial. [EAHAD 2021 abstract]. *Haemophilia : the official journal of the World Federation of Hemophilia.* 2021;27(S2):65.
6. Nathwani AC, Reiss UM, Tuddenham EG, et al. Long-term safety and efficacy of factor IX gene therapy in hemophilia B. *N Engl J Med.* 2014;371(21):1994-2004.
7. Miesbach W, Meijer K, Coppens M, et al. Gene therapy with adeno-associated virus vector 5-human factor IX in adults with hemophilia B. *Blood.* 2018;131(9):1022-1031.
8. Von Drygalski A, Giermasz A, Castaman G, et al. Etranacogene dezaparvovec (AMT-061 phase 2b): normal/near normal FIX activity and bleed cessation in hemophilia B. *Blood advances.* 2019;3(21):3241-3247.
9. George LA, Sullivan SK, Giermasz A, et al. Hemophilia B Gene Therapy with a High-Specific-Activity Factor IX Variant. *N Engl J Med.* 2017;377(23):2215-2227.
10. Le Quellec S, Dane A, Enjolras N, et al. Potential limits of AAV-based gene therapy with the use of new transgenes expressing factor IX fusion proteins. *Haemophilia : the official journal of the World Federation of Hemophilia.* 2019;25(1):e11-e18.