



IHTC HEMGENIX[®] Gene Therapy for Hemophilia B Patient Agreement & Commitment

Gene therapy is an advanced new treatment that requires teaching, understanding, and your commitment. To keep you safe and give you the best chance to benefit from HEMGENIX Gene Therapy, you must understand and commit to the required follow-up and long-term evaluation. This is true even if your Factor IX levels improve.

If you decide to take HEMGENIX, we will ask you to sign this agreement and commitment form. Before you sign, you must understand:

- What HEMGENIX is and how it works
- The possible benefits and risks of taking it
- What will be expected of you and what you will need to commit to doing
- What to expect before, during, and after taking it
- The cost of HEMGENIX and what your insurance will and will not cover
- What your other treatment options are if you change your mind

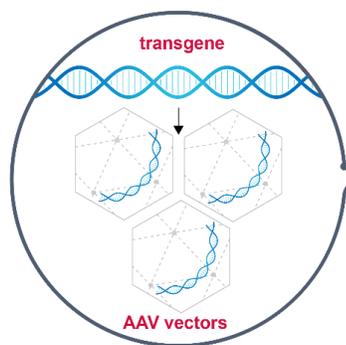
What is HEMGENIX and how does it work?

HEMGENIX may help you keep a steady level of Factor IX (FIX). People who have Hemophilia B have low FIX (sometimes Hemophilia B is called FIX deficiency). 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.

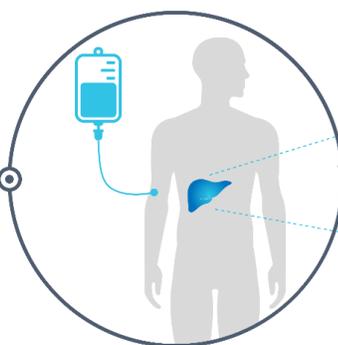
When you have Hemophilia B, your gene that makes FIX does not work properly. HEMGENIX uses a modified virus that is not dangerous to humans to deliver a working copy of the FIX gene to your liver. This gene helps your liver cells make normal FIX and release it into your blood.

- 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 cannot pass this normal FIX gene down to your children.**
- The working gene will start making FIX for you.

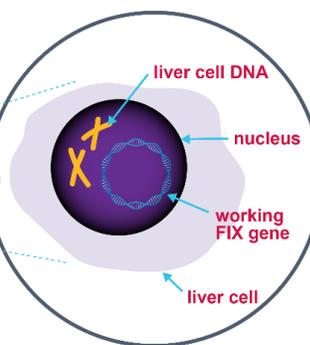
Putting the working FIX gene into the AAV vector



Delivery



Working FIX gene in liver cell



This is a short explanation of how HEMGENIX works. Your doctor will talk to you in much more detail about HEMGENIX using the **IHTC Patient Education Module for HEMGENIX Gene Therapy**.

My initials here confirm that:

- **I understand what HEMGENIX is and how it works.**
- **My doctor and I will review the IHTC Patient Gene Therapy Education Module and make sure I understand all the information.**
- **All my questions have been answered.**

Initials

What are the possible benefits and risks of HEMGENIX?

Possible benefits

People with moderately-severe to severe Hemophilia B usually have FIX levels of 5% or lower. Many people who take HEMGENIX have increased FIX levels. Studies have shown that one year after taking HEMGENIX, people had an average FIX activity level of 41.5%. Two years after taking HEMGENIX, the average FIX activity level was 36.7%.

People who are treated with HEMGENIX may need fewer or no regular factor infusions. Their bodies are making more FIX, so they have fewer bleeding symptoms from Hemophilia B. The actual level of FIX activity after taking HEMGENIX may be different for each person. Not everyone will have as much FIX activity level as people did in the HEMGENIX studies.

Possible risks

HEMGENIX is a one-time infusion, but people who take HEMGENIX will need frequent clinic visits and close monitoring for years after treatment. This is a list of the possible side effects.

Most common side effects: Infusion reactions (allergic reactions)

- 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

Possible serious side effects

Liver inflammation

- HEMGENIX targets cells in your liver. This can cause liver inflammation. Liver inflammation means your liver is swollen and irritated. This is an expected response to these cells from your immune system. Some people may need to take a medicine called a corticosteroid (like Prednisone) for a few months to reverse the liver inflammation. In clinical trials, liver function test results got worse for 24 out of 54 (44%) people. Nine (9) out of 54 (17%) people needed treatment with steroids as a result. These 9 people needed steroid treatment for an average of 80 days.

Treatment failure

- HEMGENIX gene therapy may not work for you—meaning your FIX levels may not improve. If it does not work for you, you will not be able to take HEMGENIX again because your immune system will reject the vector. You may also not be able to take any other gene therapy product in the future.

Increased risk of cancer

- Gene therapy could increase your risk for cancer. We think this risk is very low.

Unknown benefits or risks

There may be other benefits and risks of HEMGENIX that we do not know about at this time.

Safety at IHTC during the Infusion

The IHTC is committed to keeping you safe during this procedure. The IHTC clinic will have a safety response plan ready during your infusion in case you have a reaction. This safety response plan will tell clinic staff how to help you if you have a reaction to the infusion.

My initials below confirm that:

- **I understand the known possible benefits and risks of taking HEMGENIX.**
- **All my questions have been answered.**

Initials

If I take HEMGENIX, what commitments will I need to make?

Commitment to follow-up

For your safety and for the best chance for the gene therapy to work, you must follow this schedule for bloodwork and exams.

Time period	Activity	How often
First 2 weeks after infusion	Physical exam and blood test	1 time a week
3 weeks to 3 months after infusion	Blood test	1 time a week
Months 4 through 12 after infusion	Blood test	1 time a month. You might need blood tests more often if you have liver inflammation.
1 year after infusion	Physical exam and blood test	2 times a year

You can find more information about your follow-up schedule on page 8.

Commitment to staying safe

Protect your partner during sexual activity

You need to use a condom during sexual activity for at least 6 months after the infusion. This is not only to prevent pregnancy. This will also protect other people from your body fluid. We know that semen will contain the gene therapy vector for at least 6 months after the infusion. Along with condoms, you should think about using another kind of birth control if you have a partner who could get pregnant. This might include the birth control pill or an IUD.

Protect your liver

Drinking alcohol may cause or make your liver inflammation worse. It also lowers the chance that the gene therapy will work for you. The extra strain on your liver can put your health and safety at risk. **Because of the risk to your liver, you cannot drink any alcohol for at least 1 year after your infusion.**

After a year, you can drink a small amount of alcohol. You should:

- Only drink 1 drink in a single day.
- Never drink more than 3 drinks in a 7-day period. Each of these 3 drinks should be on a different day.
- You will need to follow these limits for the rest of your life.

Do not donate blood, organs, tissues, or transplant cells

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

Take care of your overall health

It is important to take care of your health after getting gene therapy. You should:

- Eat a healthy diet
- Be physically active
- Avoid alcohol
- Follow health and safety guidelines that keep you well

Staying well and keeping your liver healthy will increase the chance that the gene therapy will work for you.

Commitment to staying in contact with IHTC

It is important that you stay in contact with IHTC during your infusion and follow-up. For your safety and for the best chance for the gene therapy to work, your doctor needs to know everything going on with your health before and during the follow-up period. **Contact IHTC right away about:**

- **Any changes in your health, including**
 - **New problems**
 - **New symptoms**
 - **New medicines including herbal supplements**
- **If you have trouble doing your follow-up blood draws**
- **If you are not able to follow the expectations for alcohol use or safe sex.** This is to make sure you are safe and to have the best chances for gene therapy to work. Your doctor will talk to you about what to do next or if your treatment plan will need to change.

You can reach someone at IHTC anytime at 317-871-0000 or toll-free at 1-877-256-8837 (1-877-CLOTTER).

Commitment to following Corticosteroid treatment plan (if needed)

During the first year after your infusion, you will get follow-up labs on a regular schedule. These labs will check your blood for signs of liver inflammation. If your labs show signs of liver inflammation, you will need to have blood tests more often so that your doctor can closely watch your liver health. You may also need to start taking corticosteroids (also just called steroids) every day. If you need corticosteroids (also just called steroids), you will have to take them every day until your liver inflammation gets better.

Steroids (like Prednisone) can lower inflammation anywhere in the body. Taking them can help lower the inflammation in your liver. If you need steroids, you will have to take them every day until your liver inflammation gets better.

You must take steroids at the same time every day. Your dose will get smaller over time until you are done. **It is important for you to follow the exact schedule and instructions for your steroid treatment.** You cannot skip doses, change the dose or schedule, or stop taking them all the sudden.

In HEMGENIX trials, 9 out of 54 patients (17%) needed corticosteroid treatment after their treatment. The average length of corticosteroid treatment was 80 days.

There are many possible side effects while taking corticosteroids.

- Increased hunger
- Weight gain
- Feeling sick to your stomach (nausea)
- Acne and skin changes
- Having trouble sleeping
- Having a weakened immune system (immunosuppression)
- Mood changes and mood swings (feeling irritable, angry, or very anxious and excited)
- Mental health problems (feeling depressed or anxious, thinking about suicide)
- High blood sugar (this is usually short-term, but you may need treatment)
- If you have a seizure disorder, steroids can make it worse
- Acid reflux, ulcers, or bleeding from your stomach or small intestine
- Increased blood pressure
- Nerve damage to your eyes (glaucoma) or cloudy vision (cataracts)
- Higher risk of infection

You will need extra monitoring while you're on steroids if you have:

- Diabetes or pre-diabetes
- High blood pressure
- Glaucoma
- Mental health or mood disorders

Commitment to public health

Hemophilia gene therapy is a brand-new treatment. We need information about how it works for each person who gets it to help understand how it will work for everyone. When you share your information for this public health effort, you help guide care for people with hemophilia in the future.

Your privacy is important to us. Information that is collected for public health is anonymous. This means no one knows that it's about you. Your information cannot be linked back to any personal identifiers. Personal identifiers are things like your:

- Name
- Date of birth
- Medical record number
- Phone number
- Address

Because your information is not linked to these identifiers, anyone who looks at the information will have no way of knowing it is connected to you.

We have public health studies at IHTC that collect information to add to national data about people with hemophilia:

- ATHN Transcends National History Study
- ATHN Dataset National Database for Hemophilia Treatment Centers
- Community Counts: Public Health Surveillance Project for Bleeding Disorders

You can enroll in these studies today. When you enroll, information about your gene therapy treatment can be used for the greater good of hemophilia care.

My initials here confirm that:

- **I understand and commit to the safety and follow-up expectations described above.**
- **All my questions have been answered.**

Initials

What tests will I need to have to see if I can take HEMGENIX?

HEMGENIX screening assessments:

- Medical chart review

Your doctor will review your medical chart and history. They will look at your heart health, your HIV status (and treatment medicines if you are HIV-positive), and other medical conditions you may have now or in the past. This includes hepatitis B or C. This is to make sure it is safe for you to take gene therapy. If your doctor has concerns, they may order a heart scan or more bloodwork.

- AAV5 immunity level blood test

Since this gene therapy uses an AAV5 viral vector, we need to check if you are already immune to AAV5. If you haven't already had a blood test to check your immune response to AAV5, we will draw your blood today. This blood test will check to see if you are immune and how strong your immune response is. We will call you to tell you your result when we receive it. If your immune response to AAV5 is higher than a certain level, you will not be able to take HEMGENIX at this time.

- Liver health screening

Since hemophilia gene therapy targets cells in your liver, we need to check your liver health before you take HEMGENIX. If you haven't already had liver function tests, we will draw blood to check your liver today. If your results are out of range, your doctor may order a liver scan to do a complete check of your liver health.

- Psychosocial assessment

An IHTC social worker will go over a psychosocial assessment with you. This assessment checks your mental health status, coping skills, and any life barriers that may affect your ability to do gene therapy.

Outcome

Your IHTC doctor will tell you the results of your screening assessments and whether you are able to have HEMGENIX.

My initials here confirm that:

- **I understand the assessments described above will help decide if I can take HEMGENIX.**
- **I understand my IHTC doctor will tell me the outcome.**
- **All my questions have been answered.**

Initials

What is the schedule for the HEMGENIX infusion and follow-up?

Day of infusion

A lot of people work hard to make your gene therapy infusion happen: nurses, pharmacists, doctors, delivery drivers, financial staff, and others. **It is important for you to follow the schedule we give you and arrive to your appointment on time.** We will pick an appointment date and time with you far in advance of your infusion. Here is a timeline for your infusion day.

Time	Activity	Location
Evening before your infusion	Drive to hotel (if you live outside of Indianapolis)	Local hotel
Morning of your infusion	Arrive on time at IHTC for your appointment	IHTC clinic
1-3 hours	Gene therapy infusion	IHTC clinic
For 3 hours after your infusion	Safety monitoring in the clinic	IHTC clinic
Evening after your infusion	Second overnight in hotel (if you live outside of Indianapolis)	Local hotel
Day after your infusion	Return to IHTC for safety check-up	IHTC clinic

If you live outside the Indianapolis area, you will stay in a hotel near IHTC for two nights: the evening before your infusion and the evening after. We will arrange and pay for your hotel stay.

On the infusion day, you will spend the entire day at IHTC. You may bring your personal items like tablet, books, blanket, water bottle, or snacks to use during the day. We will pay for any meals you need while you're at the clinic on infusion day.

When you get to IHTC on the morning of your infusion, we will:

- Place intravenous lines (IVs) in your arm with a needle
- Draw blood
- Check your vital signs (heart rate, blood pressure, temperature)
- Do a physical exam

When these are done, it will be time for your infusion. The infusion will take at least 1 hour, but it could take up to 3 hours. After your infusion, you will need to stay in the IHTC clinic for at least 3 hours for safety monitoring. During safety monitoring, we will watch closely to make sure you do not have an allergic reaction to the infusion.

If you live outside of Indianapolis, you will stay at a hotel near IHTC for one more night. This is so you will be nearby in case you have a reaction or problem after the infusion. The next day, you will come back to IHTC for a safety check-up. You will need to come back to IHTC for the safety check-up no matter where you live.

After your infusion

It is important that you follow your schedule for blood tests and clinic appointments. This can affect whether HEMGENIX works for you or not. After your infusion, you will need blood tests often. You will also need some physical exams to check on your health. The blood tests will check on your liver and general health. Here is the schedule for your follow-up.

Time period	Activity	How often
First 2 weeks after infusion	Physical exam and blood test	1 time a week
3 weeks through 3 months after infusion	Blood test	1 time a week
Months 4 through 12 after infusion	Blood test	1 time a month. You might need blood tests more often if you have liver inflammation.
1 year after infusion	Physical exam and blood test	2 times a year

If your labs show liver inflammation after your infusion, you may need blood tests more often. You may also need to take a type of medicine called corticosteroids (such as Prednisone) every day until the liver inflammation gets better. You can find more information about this in the section called ***Commitment to following Corticosteroid treatment plan*** (page 5).

Safety Expectations

You will need to follow safety expectations after taking HEMGENIX. You can find details about these in the section ***If I take HEMGENIX, what commitments will I need to make?*** (page 4). The schedule for these expectations is in the table below.

Safety Expectation	How long
Use a condom during sexual activity	At least 6 months after your infusion
Do not drink any alcohol	At least 1 year after your infusion
Do not donate blood, organs, tissues, or transplant cells	Never again after your infusion
Follow your steroid treatment plan (if needed)	Every day for weeks to months

Communication with IHTC

IHTC will assign a nurse as your Care Coordinator to work with you during your care after you take HEMGENIX. It is important that you stay in close contact with your IHTC Care Coordinator after your infusion. **Contact your IHTC Care Coordinator, doctor, or other staff if you:**

- **Have any changes in your health (new problems or symptoms)**
- **Are taking any new medicines or herbal supplements**
- **Are having trouble getting your blood tests**
- **Drink alcohol**
- **Have sex without using a condom**

This is to make sure you are safe and to have the best chances for gene therapy to work. Your doctor will talk to you about what to do next or if your treatment plan will need to change.

My initials here confirm that:

- **I understand what to expect during and after the HEMGENIX infusion.**
- **I understand and commit to the safety and follow-up expectations described above.**
- **I understand and commit to stay in close contact with IHTC during my follow-up.**
- **All my questions have been answered.**

Initials

How much does HEMGENIX cost? Will my insurance cover it?

Right now, insurance companies are looking into coverage and guidelines for this therapy. We will check to see whether your insurance will cover this treatment. It may take some time for us to work with your insurance company to determine if they will provide coverage.

You will need to have insurance to get this treatment. The estimated cost for just the infusion is \$3.5 million. This amount does not include the tests and assessments you will need before the infusion. It also does not include the blood tests, clinic visits, medicines, and other follow-up you might need after the infusion.

As far as we know, there are no programs that help pay for this treatment (also called compassionate use patient assistance program). Our staff will work with you to check on your insurance coverage, understand costs that will not be covered by insurance, and find options for assistance with these costs.

My initials here confirm that:

- **I understand that IHTC will check to see if my insurance will cover HEMGENIX treatment.**

Initials

What if I change my mind about taking HEMGENIX?

Taking HEMGENIX is your choice. You do not have to take it if you do not want to. You can talk to your doctor about staying on your current treatment or looking into other treatments. You can also change your mind at any time during the pre-treatment screening process (meaning before you get the HEMGENIX infusion). If you choose not to take HEMGENIX, your other options are:

- Stay on your current treatment plan
- Talk to your doctor about changing to a new treatment plan
- Talk to your doctor about research treatment trials that are available to you

My initials here confirm that:

- **I understand that taking HEMGENIX is my choice and I do not have to take it.**
- **I can change my mind and decide not to take HEMGENIX up until the infusion.**
- **I understand what my other options are if I change my mind.**

Initials

Who can I contact if I have questions?

You can reach your IHTC Care Coordinator, doctor, or other staff by calling 1-877-256-8837 (1-877-CLOTTER) 24 hours per day, 7 days per week. You can also contact IHTC staff using Klara or your patient portal.

My initials here confirm that:

- **I understand who I can contact if I have questions or concerns during my treatment.**

Initials

Signature Page: My Agreement for Treatment and Commitment to Follow-up

By signing below, you are saying you agree to participate in HEMGENIX screening and treatment. You are also saying that you will commit to all expectations that we discuss with you. Keep a signed copy of this agreement for your reference.

Write your initials on the lines below to confirm each item listed.

_____ You understand what HEMGENIX is and how it works.

_____ Your doctor has reviewed the *IHTC Patient Gene Therapy Education Module* with you. You understand the information.

_____ You understand the known possible benefits and risks of taking HEMGENIX.

_____ You understand there may be benefits and risks of HEMGENIX that we do not know about at this time.

_____ You understand what to expect before, during, and after taking HEMGENIX.

_____ You understand and commit to the safety and follow-up expectations described in this agreement.

_____ You understand what your other options are if you change your mind.

_____ Your doctor has reviewed this agreement with you today and is signing it with you.

_____ All of your questions have been answered.

Patient printed name

Date

Patient signature

Consenting physician printed name

Date

Consenting physician signature

Witness printed name

Date

Witness signature