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# MEDICAL FACULTY ASSOCIATES

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THE GEORGE WASHINGTON UNIVERSITY

## Research Consent Form

**RESEARCH STUDY:** Safety and Dose Finding Study of Xigris (Drotrecogin alfa activated) as an anti-coagulant in End Stage Renal Disease (ESRD) patients treated with Hemodialysis (HD)

**INVESTIGATOR:** Lakhmir Chawla, M.D.  
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**Sub-Investigator:** Samir Patel, M.D.

**SPONSOR:** Eli Lilly Pharmaceuticals

**GWU IRB number:** 100416

### **Introduction**

You are invited to take part in a research study. Before you decide to be a part of this study, you need to understand the risks and benefits. This consent form provides information about the research study. A staff member of the research study will be available to answer your questions and provide further explanations. If you agree to take part in the research study, you will be asked to sign this consent form. This process is known as informed consent.

Your decision to take part in the study is voluntary. You are free to choose whether or not you will take part in the study.

### **Purpose**

The Division of Renal Diseases and Hypertension of The George Washington University Medical Center and Eli Lilly and Company (the Sponsor) are carrying out a research study to evaluate Xigris<sup>™</sup> (Drotrecogin alfa) infused during hemodialysis for the purpose of anti-coagulation (stopping the blood from clotting), and to further evaluate the safety of Xigris<sup>™</sup> (Drotrecogin alfa) for treating patients such as yourself with kidney failure receiving hemodialysis 3 times a week. The investigator (person in charge of this research study) is Lakhmir Chawla, M.D.

As a dialysis patient, you are currently receiving heparin, which is used to limit the clotting of blood during hemodialysis. Heparin is approved by the FDA for commercial use in patients with clotting diseases. Heparin is commonly used in dialysis patients worldwide. Xigris<sup>™</sup> (Drotrecogin alfa) is a different type of anti-coagulation therapy. Xigris<sup>™</sup> (Drotrecogin alfa), like heparin, can help to limit the blood from clotting, so the dialyzer you use does not clot during treatment limiting the amount of dialysis you receive. The potential advantage of Xigris<sup>™</sup> (Drotrecogin alfa) is that it also may have an effect on the body's immune system response to foreign objects that come in contact with blood (such as the dialyzer membrane). We know that the dialysis membrane stimulates the immune response of the body. We are testing to see if Xigris<sup>™</sup> (Drotrecogin alfa) can be used safely in as a blood thinner in dialysis patients.

This research projects involves an investigational drug/device. Xigris<sup>™</sup> (Drotrecogin alfa) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of severe sepsis (severe infections), but it is not yet approved for use as a blood thinner. This research is funded by (or funded in part through a grant from) Eli Lilly Company. We are asking you to participate in a study to evaluate the use of Xigris<sup>™</sup> (Drotrecogin alfa) infused during dialysis treatment as a replacement for heparin in dialysis patients. Approximately 12 subjects will participate in this study at approximately 1 site/center in the United States. A total of 12 subjects will be enrolled in this study at the George Washington University.

### **Procedures**

If you agree to take part in this research study your doctor will review your medical and laboratory records to insure that you are eligible to participate.

Your involvement in this study will consist of 1 dialysis treatment and 1 follow-up visit. The maximum length of participation is 30 days.

On the first day of the study you will receive the study drug Xigris<sup>™</sup> (Drotrecogin alfa in place of your standard therapy (heparin).

Blood samples will be drawn pre and post dialysis treatment to measure both the anti-coagulation effects of Xigris<sup>™</sup> (Drotrecogin alfa) and your levels of inflammatory markers (naturally occurring markers in your blood that are released by the body in response to a foreign substance). Blood samples will be drawn at baseline (0 minutes), 15, 30, 60, 120 and 180 minutes into treatment and post treatment. Some of the blood will be processed immediately to determine if the study drug is thinning your blood appropriately. If these blood samples show that your blood is not in the appropriate range, the dose of Xigris (Drotrecogin alfa), will be adjusted. When you receive Xigris<sup>™</sup> (Drotrecogin alfa), the study drug will be stopped when there is 60 minutes of your dialysis session remaining. This is an added precaution to make sure there is little to no drug in your system at the end of hemodialysis. Because the drug is metabolized very quickly, once we stop giving the Xigris<sup>™</sup> (Drotrecogin alfa), the drug effect goes away quickly. Blood will also be drawn as part of the follow-up visit between day 14 and day

30. Approximately 73cc of blood will be drawn during the study (approximately 5 tablespoons).

### **Potential Risks and Discomforts**

You should understand that there might be risks for your being in this study. Although Xigris<sup>™</sup> (Drotrecogin alfa) has been given to more than 5000 people with severe infections, it has not been tested for its ability to keep a blood-filtering device from clogging up.

Xigris<sup>™</sup> (Drotrecogin alfa) is expected to decrease the ability of your blood to clot, just like heparin. This condition may cause bruising or bleeding in any location of your body. Severe bleeding can be life threatening and may result in disability or death. Of the subjects that received drug for severe infection, all patients were in intensive care and received drug for 96 hours (4 days). The risk of major bleeding in this high risk group was under 4%. Animal studies have shown that Xigris<sup>™</sup> (Drotrecogin alfa) may cause bleeding when given at very high doses. These doses will NOT be used in this study. During your study participation, you will be watched closely for any signs of active bleeding. We will be drawing your blood frequently to make sure that the drug is working at the correct level: if the level is too high, we will reduce the dose. Patients at an increased risk for bleeding or a history of major bleeding will not be eligible in the study. Before this drug was used on patients with severe infections, it was tested on healthy volunteers. When used on patients who are in good health, Xigris<sup>™</sup> (Drotrecogin alfa) was found to be very safe with a risk of serious side effect less than 0.1% (Less than 1/1000). Because you are a dialysis patient, we are taking extra precautions to make sure that we are minimizing any side effects. The extra precautions include vital sign monitoring every fifteen minutes, frequent sampling of blood levels to make sure that the subject's blood is not excessively thinned, and excluding patients who have any type of bleeding risk.

As of February 1, 2003 over 5000 adult patients with severe sepsis have received Xigris<sup>™</sup> (Drotrecogin alfa).

In two clinical trials (1821 adult patients with severe sepsis), 34 (3.6%) of the patients receiving Xigris<sup>™</sup> (Drotrecogin alfa) had a serious bleeding event, compared to 18 (2.0%) of the patients receiving placebo (sugar water). During your participation, you will be monitored closely for any signs of bleeding.

In three previously performed studies, 37 healthy dialysis subjects were given Xigris<sup>™</sup> (Drotrecogin alfa) with no adverse events reported.

The disease of severe sepsis in adults may result in a patient experiencing many bad events. Adult patients with severe sepsis who have received Xigris<sup>™</sup> (Drotrecogin alfa) have experienced many of these bad events. Other than bleeding, most of these events were observed with equal or greater frequency in patients who received placebo and all of these events are believed to be associated with the patient's illness and not caused by

Xigris<sup>tm</sup> (Drotrecogin alfa) Common bad events (events occurring in 5% or more patients) that were observed a little more frequently in adult patients receiving Xigris<sup>tm</sup> (Drotrecogin alfa) than adult patients receiving placebo include diarrhea, confusion, skin ulcers, vomiting, nausea, and pain. All serious bleeding events were seen in patients with low platelet counts. Patients with low platelet counts are not allowed to be enrolled in this study.

The most common problems reported in healthy volunteers who have taken Xigris<sup>tm</sup> (Drotrecogin alfa) include headache, bruising and pain at the site of the needle stick. The most common risk reported in patients with severe sepsis was bleeding.

Some of the raw materials used to make Xigris<sup>tm</sup> (Drotrecogin alfa) are from animal sources. These sources are tested for possible germs and illnesses. In spite of testing, there is a possibility that a germ or illness for which testing is not available, or for which current tests are not sensitive enough to detect, may be present in the Xigris<sup>tm</sup> (Drotrecogin alfa) preparation. So far, the transfer of a germ or illness to a patient who has received drotrecogin alfa (activated) has not been reported.

In addition to the risks named above, Xigris<sup>tm</sup> (Drotrecogin alfa) or the study procedures may have other unknown risks.

There may also be unknown risks to an embryo, fetus, or unborn child. Women who are pregnant or breastfeeding may not take part in this study.

## **PREGNANCY/CONTRACEPTION/BREASTFEEDING**

### **1. PREGNANCY**

Pregnant women may not take part in this research study because there are no safety information on Xigris<sup>tm</sup> (Drotrecogin alfa) in pregnant patients. To determine if you are pregnant, pregnancy testing will be performed on all women capable of becoming pregnant before and during participation in this study. Even if not sexually active, all female participants will be given a pregnancy test. The only exceptions are when female participants have stopped having menstrual periods for at least one year after menopause (change of life); or have undergone sterilization surgery (tubes were tied or had a hysterectomy). If a child is conceived (created) while a female participant is taking the study drug, the child may develop birth defects. If female participants become or suspect that they are pregnant during the study, the study doctor must be notified immediately.

### **2. CONTRACEPTION**

To participate in this study, a woman must protect herself from becoming pregnant before, during, and at least 1 day after the last dose of the study drug. If you are a man and decide to take part in this study, you need to know that some drugs may cause birth

defects in children when taken by the father. To participate in this study, a man must protect his partner from becoming pregnant during the trial.

Acceptable methods of contraception while participating in this study are:

1. Total abstinence from heterosexual sex (no sexual intercourse); or
  2. Absence of menstrual periods for more than one year after menopause; or
  3. Sterilization surgery:
    - Tubes were tied in a woman; or
    - Hysterectomy (womb [uterus] was removed); or
    - Vasectomy in a man, or
  4. Use of a birth control method with a failure rate in typical use of 10% or less:
    - a. Oral contraceptives (birth control pills);
    - b. Intrauterine devices (IUDs);
    - c. Implanted or injected contraceptives (Norplant or Depo-Provera); or
    - d. Use of a condom with a spermicide.
- It is important to use these methods exactly as directed. “Failure” means that a pregnancy occurred even though a contraceptive method was used. Methods 2 through 4 described above may not protect against HIV infection, AIDS or other sexually transmitted diseases. If you need more information about this, please ask the research study staff.
  - The following methods of contraception alone are not acceptable to prevent pregnancy during the study because the failure rates with typical use are greater than 10%: diaphragm; cervical cap; vaginal sponge; or the female condom.

### **3. BREASTFEEDING**

Because the study drug may be harmful to children, women who are breastfeeding a baby may not participate in this study. When breastfeeding, the study drug may pass to your child through your milk and risk the baby’s health. You must not breastfeed during this study and for 2 days after the last dose of the study drug.

#### **Potential Benefits**

You may not benefit directly from this study. However, this research may, in the future, provide additional information on the use of Drotrocogin alfa (activated protein C) in dialysis patients. Although there are no guarantees, the potential advantage of Drotrocogin alfa as given in this study, is that by administering the study drug, both the natural clotting factors and inflammatory markers may be decreased.

#### **Alternative Therapies**

If you decide not to participate in this study, alternative medical therapy is available to you to control your blood clotting. You will receive all standard therapy and medical

care that is provided for patients on dialysis related to chronic renal failure, whether or not you participate in this study.

An alternative therapy for the study drug heparin which is an anti-coagulant (stops your blood from clotting). You may already receive this medication during each dialysis treatment. Your treatment will depend upon the policy of your own hospital/clinic, and so you should discuss this with Dr. Chawla.

### **Consent for Use/Disposal of Blood**

By signing this consent form, you consent to the use of your blood for this research and to the disposal of any remaining blood after its use in this research or if it is determined to be unsuitable for use in this research.

### **Cost/Reimbursement**

We do not anticipate that you will incur any additional cost if you participate in this study. You will receive Xigris<sup>tm</sup> (Drotrecogin alfa) free of charge. You will not be charged for any extra doctor's visits (such as a physical), blood work, tests or procedures during this study. We will reimburse the costs of your travel or parking for study visits.

### **Compensation**

No financial compensation (payment) is available for participants in this study.

Materials/data obtained from you in this research study may lead to new inventions or products to be used for commercial purposes. It is the policy of GWU not to provide financial compensation to you if such new inventions or products are developed.

### **Compensation for Injury**

Taking part in this research study may result in injury or harm to you. (This was explained under the section entitled, "POTENTIAL RISKS.") If you require immediate medical care and are not a hospitalized patient, you should seek immediate medical treatment at the George Washington University Hospital (Take your informed consent form with you). Otherwise, the investigator will take care of you or help you get the care you need. You will be sent a bill for whatever medical care you receive. Payment for such costs will be your responsibility. Your bill should be sent to your health insurance for payment.

The George Washington University and Hospital will not pay for the care. The Medical Faculty Associates and Gambro Healthcare will not pay for your care. Likewise, The George Washington University and Hospital, the Medical Faculty Associates nor Gambro Healthcare will not pay you for pain, worry, lost income, or non-medical care costs that might occur from taking part in this research study.

If you believe that you have a research-related injury, further information concerning the availability of compensation or treatment can be obtained from Dr. Lakhmir Chawla at (202) 715-4570.

### **Confidentiality**

Your information will be kept as confidential as possible. Access to study records will be limited to those who need the information for purposes of this study, as well as your health care providers should they need access to the information. All records are kept in a secure location and access is limited to research study personnel.

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. However, your identity will not be disclosed, unless you give the appropriate authorization.

### **Privacy**

Federal law requires that hospitals, researchers and other healthcare providers (like physicians and labs) protect the privacy of health information that identifies you. This kind of information is known as “protected health information” or “PHI.” This section tells you your rights about your protected health information in the study. This section also lists who you let use, release, and get your protected health information. You are free to not allow these uses and releases by not signing this form. If you do that though, you cannot participate in the study.

Protected health information that may be used and released (disclosed) in this study includes information such as:

- This consent form;
- Your age, race, gender, height and weight;
- Your history of medical conditions including heart, lung and kidney disease, or other significant conditions such as diabetes, cancer or previous surgeries;
- Your vital signs and treatments and medications you are given during the study;
- Laboratory results of your blood tests including blood cell counts, and platelets (hematology), creatinine and blood urea nitrogen (chemistry); and blood clotting tests (coagulation).

By signing this form, you allow the use, sharing, copying, and release of your protected health information to carry out the study by:

- the Study Doctor and his research team.

You also allow the Study Doctor and his research team to release your health information to:

- GWU Institutional Review Board (“IRB”) or its authorized representatives, as well as representatives of the Office of Human Research Protections (OHRP) who

- may review your records to ensure that your rights as a research subject are protected;
- Regulatory agencies such as the U.S. Food and Drug Administration (FDA) to review data on the safety and effectiveness of the product that is being tested in this Study and other Federal and state agencies that regulate research
  - Accrediting agencies and legal counsel
  - Clinical staff who are not involved in the study who may become involved in your care, if it might be relevant to your care; and
  - GWU, GWU Hospital or GWU MFA workforce who are involved with the research;

### **Withdrawal from the study**

Your participation in this research study is voluntary. You may decide not to begin or to stop this study at any time. Your care and relations with the health care providers at The George Washington University Medical Center and Hospital will not be affected in any way. You will be told of any new information about the research study that may cause you to change your mind about participation. You may also be withdrawn by the Principal Investigator (study doctor), by Eli Lilly Inc. or by the FDA without regard to your consent. Specifically, you can be withdrawn from the study if you are unable to comply with the study protocol, or do not adhere to the safety instruction during the treatment period.

You should let the doctor in charge of the study know if you decide to stop the study early. You may be asked to visit the study site for a final examination for your safety and return the study drug if you decide to stop early. You may be asked to undergo some laboratory tests and physical examinations that the study doctor considers necessary at the time of withdrawal. This evaluation is for your safety and protection in case of unexpected side effects.

### **Questions**

If you experience a side effect or injury that may be related to this study or if you have an unscheduled visit for medical care for any reason, please contact Lakhmir Chawla by telephoning 202-715-4570 during a workday or 202-715-6141 at night or on weekends. If you have questions about the procedures of this research study, please contact Lakhmir Chawla by telephoning 202-715-4570 during the workday. If you have questions about the informed consent process or any other rights as a research subject, please contact the Office of Human Research at The George Washington University, (202) 994-2715.

**Signatures**

After you sign this Consent Form, the research team will provide you with a copy. Please keep a copy of this document in case you want to read it again.

\_\_\_\_\_  
Participant (Print Name)                      Signature                      Date

\_\_\_\_\_  
Person Obtaining Consent                      Signature                      Date  
(Print Name)

**Investigator Statement**

I certify that the research study has been explained to the above individual by me or my research staff including the purpose, the procedures, the possible risks and the potential benefits associated with participation in this research study. Any questions raised have been answered to the individual's satisfaction.

\_\_\_\_\_  
Investigator                      Signature                      Date  
(Print or type name)

**DO NOT SIGN AFTER THE EXPIRATION DATE OF: 11 / 30 / 2010**

