

TIGECYCLINE  
Protocol 3074A1-300-CA

### INFORMED CONSENT TO PARTICIPATE IN A MEDICAL RESEARCH STUDY

**Title of protocol:** A MULTICENTER, RANDOMIZED, DOUBLE-BLIND COMPARISON OF THE SAFETY AND EFFICACY OF TIGECYCLINE WITH THOSE OF VANCOMYCIN WITH AZTREONAM TO TREAT COMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS IN HOSPITALIZED PATIENTS

**Protocol:** 3074A1-300-CA (Incorporating Protocol Amendment 1)

**Sponsor:** Wyeth Research & Wyeth-Ayerst Canada Inc.

**Investigator:** \_\_\_\_\_

### DESCRIPTION / PURPOSE OF THE STUDY

You are invited to participate in a medical research study involving the use of an experimental antibiotic, tigecycline, or a combination of approved antibiotics to treat your skin infection.

Your doctor has determined that you have developed a complicated skin and/or skin structure infection. The standard treatment for your skin infection is the administration of infection-fighting drugs called antibiotics.

The purpose of this study is to compare the safety and the effectiveness of tigecycline with those of a combination of antibiotics, vancomycin and aztreonam, in treating hospitalized patients with complicated skin and skin structure infections. These antibiotics will be given intravenously (through a vein).

Approximately 500 subjects will participate in this study at approximately 80 centers in the United States, Canada and Latin America. Of the 500 patients who enter the study, ½ will be randomly assigned (like flipping a coin) to receive the tigecycline, and ½ will be randomly assigned to receive vancomycin and aztreonam. Your study doctor will not know which test article you are receiving while you are participating in the study, but this information will be available if it should be needed.

The experimental dosage of tigecycline consists of: a one-time dose of 100 milligrams (mg) of tigecycline followed by 50 mg every 12 hours for a total daily dose of 100 mg thereafter. Following the completion of this infusion, you will receive a second infusion of 100 milliliters (ml) saline. If you receive vancomycin and aztreonam, you will receive 1 gram (g) vancomycin and 2 g aztreonam every 12 hours, given as 2 infusions as well. If the organism that is causing your skin infection is not sensitive to aztreonam (based on your culture results) your study doctor may choose to discontinue the aztreonam (or if you are randomized to the tigecycline arm of the study, the accompanying saline infusion) and continue the vancomycin.

The duration of test article administration will depend on the seriousness of your infection as determined by your study doctor. You will be given the test article for 5 days, but no more than 14 days. If your skin cultures (tests to determine the type of infection) indicate that the bacteria causing your infection are resistant (the antibiotics won't fight the bacteria) to tigecycline, or vancomycin or aztreonam, your study doctor may stop your study drug and switch you to other

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antibiotic therapy. If your study doctor decides that you are able to be discharged from the hospital, but still require intravenous antibiotic therapy, you may be given the antibiotic at home, administered by a home health care registered nurse.

#### DURATION

You will participate in the study for approximately 4 to 6 weeks. This period includes a 1-day screening period, up to 2 weeks of test article administration, and a follow-up visit no sooner than 2 weeks after the test article is discontinued.

#### PROCEDURES

Before you can start to receive the test article, you will have the following tests or procedures to determine whether or not you are able to participate in the study:

1. A review of your medical history and a physical examination.
2. Measurements of height, weight, blood pressure, heart rate, and temperature.
3. Blood samples will be taken for routine blood tests. Two additional sets of blood samples will also be obtained to check if there are any bacteria in your blood. The total amount of each blood sample will be about 5 mL (one teaspoon).
4. A sample will also be taken from your skin infection site. A small amount of fluid, pus or tissue will be obtained by either withdrawing the material through a needle or scraping the affected area.
5. If you are a woman of childbearing potential, a blood or urine sample will be taken to determine whether you are pregnant. If the pregnancy test is positive, you cannot participate in the study.
6. An imaging x-ray such as bone scan, computerized axial tomography (CAT) scan or Magnetic Resonance Imaging (MRI) may be done if your study doctor suspects (and needs to rule out) that the infection may involve the bone.

A CAT scan takes 30 to 90 minutes, depending on the body part to be scanned. If a contrast medium will be used, you must not eat or drink anything for 4 hours before the test, and remove all jewelry. A tourniquet will be applied to your arm and a radioactive isotope will be injected. A 2- to 3-hour waiting period follows injection of the isotope. During the test, you will lie on your back on an x-ray table. A strap will be placed across the body part to be scanned, to prevent movement so that the x-ray will be clear. The table will then slide into a large, tunnel-shaped machine. When the CT scan is finished, you may immediately resume your usual activities and diet. When the contrast medium is injected during the CT scan, you may experience nausea, flushing, warmth, and a salty taste. You might be allergic to the contrast medium. You must not move during the test, but relax and breathe normally. You might be uncomfortable while you are in the tunnel-shaped machine. Some patients have felt claustrophobic during this test. You will be exposed to radiation during this test.

For a bone scan, prior fasting is not necessary. However, you should avoid eating a meal or drinking large amounts of fluids before this test. After a tourniquet is applied to your arm, a radioactive tracer will be injected into a vein. It will be necessary to wait 2-3 hours after the injection before the scan can be performed. You may be asked to drink several glasses of water during this waiting time. During the test, you will lie on your back on a table within the scanner, and must be as still as possible during the test. You may be asked to assume various positions on the table. The scanner moves slowly back and forth, recording images

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for about 1 hour. After the test is finished, you should drink plenty of fluids. The scan itself is painless, but the tourniquet and injection of the isotope may cause discomfort. You will be exposed to radiation during this test.

MRI is a technique which creates high resolution images of the body without the use of x-rays. The technique uses a magnet and radio frequency waves, similar to those used in an AM/FM radio. Patients with brain aneurysm clips, metallic foreign bodies in the eye, very recent surgery, pacemakers or cochlear implants are contraindicated. The technologist must be notified if pregnancy is suspected.

7. A photo of your skin infection may be taken.
8. You will undergo a 12 lead electrocardiogram (ECG) to assess the electrical activity of your heart.

If you are found to be eligible based on these tests, the following will occur:

1. You will receive intravenous infusions twice a day over a period of approximately 2 hours.
2. The period will last at least 5 days but not more than 14 days.
3. During the period, your temperature and blood pressure will be taken and your skin infection will be assessed on a daily basis.
4. Blood samples will be taken on Days 3 and 7, and on the last day of treatment.
5. Not more than 100 mL (6 ½ tablespoons) of blood will be drawn for study purposes throughout the 4 to 6-week study period.
6. You will have a second ECG performed during the study assess the electrical activity of your heart.
7. You will be asked to return to your study doctor's office for one additional visit approximately three weeks after the infusions have stopped. You may be reimbursed (up to \$\_\_\_\_.00) for your travel to and from the study doctor's office. It is essential that this follow-up visit be completed. The blood tests will be repeated at the follow-up visit. During this visit, your skin infection will also be reevaluated and a final ECG will be performed.

**RISKS ASSOCIATED WITH THE STUDY**

All medications have the potential to cause side effects. There may be risks that we do not know about. However, precautions will be taken to reduce the risks. You should not participate in this study if you have any of the following conditions:

- a history of allergies to tetracycline, or a tetracycline-like drug, or vancomycin or aztreonam-like drugs
- severe kidney, heart, lung, or liver disease
- a history of bleeding disorders

You should discuss all of your past and present diseases and allergies with your doctor. If you have any questions regarding diseases and/or allergies that you may have had in the past, ask your study doctor.

The most common side effects of tigecycline are nausea, vomiting, diarrhea, constipation, stomach upset, headache, dizziness, itching, rash and swelling of the hands and feet. Some patients have had increases on the enzymes of the liver. Pain can occur at the site where the medication is injected into your vein. In addition, the following symptoms have been reported:

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severe rash, severe diarrhea called colitis, pulmonary edema (excess fluid in the lungs), and decreased kidney function.

Tigecycline is related to an antibiotic called minocycline and a group of antibiotics called the tetracyclines. The most common side effects that occur with the use of minocycline and tetracyclines are the loss of appetite, nausea, vomiting, diarrhea, yeast infections in the anal and genital areas, and rashes. Other rare reactions have been reported including photosensitivity (a severe sunburn), liver failure, and pseudotumor cerebri (benign intracranial hypertension) with headache and blurred vision as the usual manifestations. This condition and related symptoms usually resolve after discontinuation of the tetracycline, however, the possibility of permanent impairment exists.

Tetracyclines can interact with anticoagulants, commonly called "blood thinners" such as warfarin. Tetracyclines can also interfere with the action of penicillins and oral contraceptives ("birth control").

The most common side effects of vancomycin are usually related to the infusion and may include, but are not limited to: an allergy (shortness of breath; closing of your throat; hives; swelling of your lips, face, or tongue; rash; or fainting); or pain and muscle spasm of the chest and back. Numbness and a rash may appear in the arm used for study drug administration. Patients may also experience little or no urine, decreased hearing or ringing in the ears; or severe watery diarrhea and abdominal cramps. Less frequently nausea, dizziness, chills, blood cell abnormalities or a rash may be seen.

The most common side effects of aztreonam include, but are not limited to, inflammation and discomfort at the infusion site, diarrhea, nausea and/or vomiting, and rash. Less frequently low blood pressure, changes in the electrical activity of the heart (ECG abnormalities), blood cell abnormalities, wheezing, difficulty breathing, chest pain, dizziness, confusion, seizure, general body weakness, fever and headache have been reported.

The experimental drug used in this study may involve other risks that are not known at the present time.

Any medication, including the antibiotics used in this research study, can cause allergic reactions including anaphylaxis in which there can be shock and breathing problems severe enough to be life-threatening.

The risks of drawing blood and giving the antibiotics through a vein include pain and bruising at the puncture site. Fainting may occur. Infection at the site where blood is drawn and/or at the site where your intravenous needle was inserted could occur. If you have x-rays you will be exposed to radiation.

You will be informed of any significant new information that could affect your willingness to continue to participate in the study.

**WOMEN OF CHILDBEARING POTENTIAL ONLY**

The medications used in this study may involve currently unforeseeable risks to pregnant women, the embryo, the fetus, or to children of nursing women. However, tetracycline class antibiotics can cause fetal harm when administered to a pregnant woman. The use of drugs in

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the tetracycline class during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). Enamel damage has been reported. Birth defects have also been reported. For this reason, all women of childbearing potential are required to undergo pregnancy testing before entering the study and, if they are sexually active, to refrain from sexual relations or to use a medically acceptable contraceptive throughout the study. Tetracyclines can interfere with the action of oral contraceptives ("birth control").

A woman of childbearing potential is defined as one who is biologically capable of becoming pregnant. This includes a woman who is using contraceptives or whose sexual partner is either sterile or using contraceptives.

If you miss a period or think you might be pregnant during the study, you must notify the study doctor immediately so that you can be withdrawn from the study. If you become pregnant at any time during the study or within 5 weeks after your last dose of the antibiotic (completion or dropout) and your pregnancy is carried to term, the study doctor will ask to follow the course of your pregnancy and delivery as well as the condition of your infant at birth.

Tigecycline, vancomycin and aztreonam are secreted in breast milk. You should not enroll in this research study if you are breast feeding your child.

Men who are participating in this research study need to understand the danger of taking a drug whose effects on a fetus are unknown.

#### **BENEFITS ASSOCIATED WITH THE STUDY**

You and society may benefit from any experimental research. Such benefits include the possibility that your condition may improve and that this study may help develop a new therapy for others with similar conditions.

#### **PAYMENT**

You will not be paid for your participation.

#### **ALTERNATIVE THERAPY**

Other treatments that use different types and combinations of antibiotics are available to treat your condition. Some examples are ciprofloxacin, ceftioxin, and ampicillin-sulbactam. Their effectiveness varies according to their suitability for an individual patient. You do not have to participate in this study to be treated for your skin infection.

#### **REVIEW OF RECORDS; CONFIDENTIALITY**

All medical information will be confidential unless disclosure is required by law. Only the study physician and authorized study personnel, the sponsoring company, Institutional Review Board (IRB) or Independent ethics committee (IEC), the Health Products and Food Branch (HPFB), the US Food and Drug Administration (FDA), and other regulatory agencies will have access to your medical records. They are required by law, however, to handle this information in a strictly confidential manner.

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Information from this study will be submitted to the sponsoring company and to government regulatory agencies, but your name will not be identified in such records since you will be identified only by initials and code number in any document that leaves the research center. Any report published as a result of this study, which may include photographs, will not your identity.

#### RIGHT TO ASK QUESTIONS AND TO WITHDRAW FROM THE STUDY

- If you have any questions concerning this study, call \_\_\_\_\_ at (\_\_\_\_) \_\_\_\_-\_\_\_\_.
- If you think you have experienced a research-related injury and if you have any questions concerning the availability of medical care call \_\_\_\_\_ at (\_\_\_\_) \_\_\_\_-\_\_\_\_.
- If you have any questions about your rights as a research subject, call \_\_\_\_\_, of the Institutional Review Board at \_\_\_\_\_ (facility) at (\_\_\_\_) \_\_\_\_-\_\_\_\_.

#### RESEARCH-RELATED INJURY

If you become injured during this study, and your injury is a direct result of the effects of the test article (any drug, co-medication, placebo, active comparator, or device) or study procedures, reasonable medical treatment will be provided by [Name of Institution]. The cost of this treatment will be paid by the sponsor, Wyeth Research.

#### COSTS

You will not incur any additional costs as a participant in this study.

#### VOLUNTARY PARTICIPATION AND CONDITIONS OF WITHDRAWAL

Your participation in this study is voluntary. You may refuse to participate or you may withdraw at any time without penalty or loss of benefits to which you are otherwise entitled. Your study doctor may withdraw you from the study at any time he or she feels it is in your best interest, without first obtaining your consent.

If you should leave the study for any reason, you must return all unused test articles. You may be asked questions about your experience with the test articles. You also may be asked to undergo whatever laboratory tests and physical examinations the study doctor considers necessary.

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### CONSENT

I, \_\_\_\_\_, have read and understood the preceding information.  
I agree to participate in this research study. I do not waive my legal rights by signing this  
consent form. I will receive a signed copy of this consent form.

\_\_\_\_\_  
Printed name of Subject

\_\_\_\_\_  
Signature of Subject

\_\_\_\_\_  
Date and time of signature

\_\_\_\_\_  
Printed name of Parent / Guardian / Representative

\_\_\_\_\_  
Signature of Parent / Guardian / Representative

\_\_\_\_\_  
Date and time of signature

\_\_\_\_\_  
Printed name of Person Administering Consent

\_\_\_\_\_  
Signature of Person Administering Consent

\_\_\_\_\_  
Date and time of signature

Subject number: \_\_\_\_\_

Subject initials: \_\_\_\_\_

Subject date of birth: \_\_\_\_\_

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