

Palmetto Clinical Research

INFORMED CONSENT TO PARTICIPATE AS A RESEARCH SUBJECT

Lay Title: An Investigational Drug called Doripenem in Patients with  
Complicated Lower Urinary Tract Infection

*Sponsored by Peninsula Pharmaceuticals, Inc.*

**Protocol DORI-03: Phase II, Double-Blind, Dose-Finding Study of Intravenous  
Doripenem in Complicated Lower Urinary Tract Infection or Pyelonephritis**

You are being asked to participate in a research study. The purpose of this document is to provide you with information to consider in deciding whether to participate in this research study. Consent must be based on an understanding of the nature and risks of the treatment, device or procedure. Please ask questions if there is anything you do not understand. Your participation is voluntary and will have no effect on the quality of your medical care if you choose not to participate.

I \_\_\_\_\_  
of \_\_\_\_\_

agree to be tested to see if I am suitable to participate in this clinical research study known as "DORI-03", titled: "Phase 2, Double-Blind, Dose-Finding Study of Intravenous Doripenem in Complicated Urinary Tract Infection (cUTI) or Pyelonephritis". I will allow the medical staff to perform the following tests or medical procedures to see if I qualify.

- Take blood samples
- Take urine samples
- Test my heart function using a test called an electrocardiogram or ECG
- Record my vital signs (pulse, blood pressure, temperature, breathing rate)
- Ask me questions about my medical history
- Do a physical examination
- Take blood samples to test for pregnancy if I am female

\_\_\_\_\_  
Signature Date: \_\_\_\_/\_\_\_\_/\_\_\_\_

\_\_\_\_\_  
Signature (Witness) Date: \_\_\_\_/\_\_\_\_/\_\_\_\_

\_\_\_\_\_  
Name (Print) (Witness)

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## WHAT IS THE PURPOSE OF THIS STUDY?

You have been asked to consider taking part in this study because the medical staff believes that you have a complicated urinary tract infection. This study is being done to find out if doripenem, a new antibiotic to be used for treatment of severe infections, is safe and can cure complicated urinary tract infections like the one you have. Tests will also be done to find out if doripenem can kill the bacteria that are causing your infection. This drug has been given to Japanese people who had infections similar to yours. It did help to cure their infections and it was safe for them to use. This study will test doses of doripenem that are higher than those studied in Japan.

## ARE THERE ANY CONDITIONS FOR PARTICIPATION?

In order to be considered for this study you should be over the age of 18 years, have a complicated urinary tract infection, or a condition called "pyelonephritis." The medical staff will judge if you are suitable for the study at screening, before the first dose of the drug is given.

## DO YOU HAVE TO TAKE PART?

This is a research study and your participation is entirely voluntary. This means that it is up to you to decide whether or not to take part. If you decide not to take part in this study, your doctor will treat your urinary tract infection with another antibiotic that he/she decides will be best for curing your infection.

If you do decide to take part, you will be given this information sheet to keep and will be asked to sign a consent form. Even after you sign the consent form, you do not have to take part in the study and may withdraw at any time; however, if you have taken the study drug, you must return to this facility for a safety visit (i.e., a physical examination and possibly extra safety blood tests) about one month after the last dose you received.

The doctor involved in the study and the Sponsor (the company that is testing the drug) have the right to withdraw you from the study at any time for reasons such as safety, uncooperative behavior, not following the study plan, or adverse events that make it unsafe for you to receive any more treatment with the study drug. The study may be stopped early by the Sponsor, the doctor involved in the study, or the local research ethics committee.

If you need information about your rights as a research subject, you may contact:

**Trident Regional Medical Center  
Institutional Review Board  
9330 Medical Plaza Drive  
Charleston, SC 29406  
843-797-4549**

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## WHAT IS THE DRUG BEING TESTED?

Doripenem is the drug being tested in this study. It is a new antibiotic drug.

## HOW MANY VOLUNTEERS ARE INVOLVED IN THIS STUDY?

This study will involve about 120 volunteers in 25 medical centers. Locally we expect to enroll approximately 5 volunteers. Half of the people who take part will receive doripenem at 250 mg every eight hours and half will receive doripenem at 500 mg every eight hours for 7 to 14 days. You will be hospitalized for at least the first 9 infusions of study medication (approximately 3 days) and may be discharged from the hospital if arrangements for continuing the medication as an outpatient can be made. If you finish all the treatment the doctor prescribes, you will have to return to the study center twice after you finish your treatment; the first visit will occur 5 to 9 days after the last dose of study medication and the last visit will occur 28 to 35 days after the last dose of study medication. These visits are to check if the study medication cured your infection and to determine any side effects from the study medication. If you withdraw from the study before you receive all the medication the doctor prescribes, you must return to the study center about one month after you receive the last dose of medication.

## WHAT WILL HAPPEN IF YOU TAKE PART AND WHAT WILL YOU HAVE TO DO?

### SCREENING VISIT

Today you will have a screening visit. The doctor will explain the study to you, ask you questions about your health, and do a physical examination. Certain tests will be done for the purposes of this study; these tests include an electrocardiogram (ECG - probes are placed on your chest, arms and legs to perform a recording of the electrical impulses of your heart), blood and urine tests to determine organ function, (including a blood test for pregnancy if you are female) and a urine test to identify the bacteria that is causing your urinary tract infection.

If you agree to take part in this study and you are selected, you will be randomized (like tossing a coin) to receive one of two dose levels of doripenem. You will not be told which dose level of study drug you are receiving. Because the study is 'double blind', the doctors and nurses treating you will not know which dose you will be receiving either. However, there are emergency procedures which will allow your doctor to know which dose level you are receiving, if it becomes necessary.

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## WHAT TESTS WILL BE DONE DURING THE STUDY?

### TREATMENT PERIOD

Once you have been selected for the study and agree to take part, an IV cannula (tube) will be put into a forearm vein on each arm. You will receive doripenem as intravenous infusions through one of the cannulas three times daily for at least seven days. The other cannula will be used to take blood samples throughout the treatment period. Each infusion will last about 60 minutes. At various times throughout the study, certain tests and procedures will be done to monitor your safety and the effectiveness of doripenem on your infection. These procedures include:

- Physical examinations
- Vital signs (blood pressure, heart rate and breathing rate)
- Body temperature measurements three times a day
- 12-lead ECGs (non-painful recordings of the electrical impulses generated by your heart)
- Blood and urine samples taken: Blood samples will be taken from the IV cannula, opposite of the arm that the study medication is infused. The total amount of blood that will be drawn will not exceed 200 mL, which is less than what is drawn in a blood donation.
- You will also be asked to report all side effects as soon as possible after you notice them and inform your doctor or nurse of any other medication that you may be taking during this study period.

### FOLLOW-UP PERIOD

Once the treatment is complete, you will need to return to the clinic twice. The first follow-up visit will occur 5-9 days after your last study medication infusion and the last follow-up visit will occur 28-35 days after your last study medication infusion. Certain tests and procedures will be done to monitor your safety and the effectiveness of doripenem on your infection. These procedures include:

- Physical examination
- Vital signs (blood pressure, heart rate, and breathing rate)
- Blood and urine samples
- You will be asked to report all side effects that have occurred during the study period and inform your doctor or nurse of any other medication that you may be taking during this study period.

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## WHAT ARE THE SIDE EFFECTS OR RISKS OF TAKING PART?

Doripenem is a new drug that may be useful in treating severe bacterial infections. More than 600 people have received doripenem to date (healthy volunteers and patients). Doripenem has been generally well tolerated. The following adverse effects have been reported in clinical studies:

Anorexia (not wanting to eat), dizziness, diarrhea, cough, constipation, fever, headache, lethargy (tiredness), mild to moderate elevations of liver function tests, loose bowel movements, malaise (generally feeling bad), nausea, numbness of tongue and limbs, pain at the infusion cannula site, sore mouth, sore tongue, stomach pain, tremor, raised and lowered white blood cell counts (cells involved in inflammation & fighting infections), rash, and runny nose.

Adverse effects seen with other antibiotics of the same type may be seen with doripenem. These include nausea, vomiting, diarrhea, taste disturbances, hearing loss, blood disorders, mild elevations of liver function tests, fever, rashes, allergic reactions, convulsions and infusion site irritation

There may be risk of potentially dangerous side effects to an embryo or fetus. Pregnancy should therefore be avoided. Patients who are pregnant, planning to become pregnant, or mothers that are currently breast-feeding should not participate in this study. Should you become pregnant during the course of the trial, you must inform the investigator immediately and study medication must be terminated.

The doses planned in this trial have been given before and have been generally well tolerated.

In animal studies, very high doses of doripenem have caused kidney damage. This is similar to kidney damage seen with other drugs of this type of antibiotic at high doses. In comparison to other antibiotics of this type, doripenem was less toxic to the kidneys than some and slightly more toxic than others. The doses that caused kidney damage were much higher than the doses that you will receive in this study.

Additional EKGs are done in this study to evaluate a potential concern of an abnormal electrical impulse of the heart that was noted only in early dog studies. These abnormalities, however, were not observed in a Phase I study in 24 healthy human volunteers who received daily doses of doripenem equal to or higher than those doses to be administered in this study.

Animal experiments have suggested that doripenem should be safe given in the doses to be used in this study. Animal experiments, however, do not always predict what will happen when the drug is given to humans, so you will be closely observed during the study for any sign of adverse effects and some effects may be unpredictable. If we become aware of any new information during the study, regarding the safety of the study drug, we will tell you so that you may decide whether or not you want to stay in the study.

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Almost all drugs can cause severe rare reactions that may be life-threatening (e.g., bleeding in the stomach or intestine following aspirin and severe allergic reactions following penicillin).

As with any drugs, there is a risk that a rare or previously unknown side effect will occur.

#### **WHAT ARE THE OTHER POSSIBLE DISADVANTAGES AND RISKS?**

During the study you will have blood drawn frequently. The risks associated with the blood drawing are mild pain from the needle sticks and a chance of bruising or infection at the site used for blood drawing. In order to avoid the use of several needles on days when blood sampling is frequent, the medical staff will attempt to insert a tube in a vein in your forearm, called a cannula.

#### **WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART?**

There is no guarantee that you will receive any benefit from this study. Doripenem has been shown in laboratory studies to kill bacteria that typically cause urinary tract infection. This study is to evaluate how well this occurs in humans.

#### **WHAT IF NEW INFORMATION BECOMES AVAILABLE?**

Sometimes during the course of a research project new information becomes known about the drug that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the study. Also, your study doctor might consider it to be in your best interest to withdraw you from the study if this new information suggests that the drug could be harmful to you.

#### **WHO DO I CONTACT IF I WOULD LIKE MORE INFORMATION, OR IF I HAVE ANY PROBLEMS?**

If you need any information, or have any problems, concerns or questions about the study please contact any of the following people:

**Palmetto Clinical Research**  
201 Oakbrook Lane, Suite 255  
Summerville, SC 29485  
(843) 851-7098 or (843) 851-2000

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**WHAT IF SOMETHING GOES WRONG?**

If you have any adverse drug experience resulting directly from taking part in this study, you will be treated free of charge. If you feel you may have a research-related injury or illness, you should contact the following people:

**Palmetto Clinical Research**

**201 Oakbrook Lane, Suite 255, Summerville, SC 29485**

**(843) 851-7098 or (843) 851-2000**

**WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?**

Throughout this study your doctors, nurses, and other staff members will record information about you in forms (known as "case report forms"). This personal information will include information about your health and your demographic details (such as your date of birth, your sex, and your ethnic origin). All records and all other information about you written on the case report forms will be identified by your initials and a subject number, not your full name.

Information collected about you will be kept and may be included in reports that will be sent to authorities in the United States of America or in other countries in the world so that one day the study medicine may be available to all patients suffering from the illness this drug treats. Your information may also be passed to authorized personnel including: independent auditors, staff of Sponsor and its group of companies, and the Food and Drug Administration (FDA). Such authorized personnel may examine your records and information and make copies. Sometimes your original medical records will need to be examined. Personnel working on the study will inspect your medical notes, for the purpose of checking whether the information about you recorded on the case report forms is correct. This is a regulatory requirement. Your notes will be treated in strictest confidentiality.

Data obtained from the study may be published in medical journals and presented at international meetings. In such cases your name will not be used.

**IS THERE INDEPENDENT ETHICAL REVIEW OF THE STUDY?**

The study will be conducted under Good Clinical Practice guidelines (an international ethical and scientific quality standard for clinical studies involving human subjects). The study will be submitted to the local Institutional Review Board (IRB) and will only begin after the committee has approved the ethics of the study.

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**PAYMENT FOR TAKING PART IN THIS STUDY**

You will not be paid for taking part in this study; however, all study related medical treatment will be free of charge. You and/or your insurance company will be responsible for costs related to your hospitalization. Study related medical treatment that you will not be charged for includes: study specific laboratory tests, physical exams by the study physician, study physician office visits, study related electrocardiograms, study medication, and study related home health visits. You will also be reimbursed for reasonable expenses, e.g., your travel costs to and from the study center.

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**CONSENT FORM FOR PARTICIPATION IN RESEARCH PROJECTS AND  
CLINICAL TRIALS**

I have had the opportunity to ask the study doctor any questions concerning the study in private. I have been given a copy of the background information and consent form and have read and understood this document.

I(name) \_\_\_\_\_

of(address) \_\_\_\_\_

\_\_\_\_\_

hereby voluntarily consent to take part in the above study, the nature and purpose of which have been explained to me. Any questions I wished to ask have been answered to my satisfaction. I understand that I may withdraw from the study at any stage without necessarily giving reason for doing so and this will in no way affect the care I receive as a patient.

SIGNED (Volunteer) \_\_\_\_\_ Date: \_\_/\_\_/\_\_

I hereby confirm that I have explained the nature of the above medical study to the volunteer named herein. Specifically, I have explained the nature of any known side effects, and the risks involved.

SIGNED (Doctor) \_\_\_\_\_ Date: \_\_/\_\_/\_\_

Name (Print) (Doctor) \_\_\_\_\_

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