

INFORMED CONSENT

A Multicenter, Randomized, Double-Blind, Comparative Study of Oral HMR3647 (800 mg once daily) Versus Oral Cefuroxime Axetil (500 mg twice daily) for Outpatient Treatment of Acute Exacerbation of Chronic Bronchitis in Adults

HMR3647A/3007

Investigator Name: _____

You are being asked to participate in a clinical research study. However, before you give your consent, you must read the following information. Once you have read the information, please ask any questions necessary for you to understand what participation in this study will involve before you sign and date the form.

Purpose and Design of the study: HMR 3647 is an investigational (not approved by the Food and Drug Administration, FDA) antibiotic drug. The purpose of this research study is to evaluate the safety and effectiveness of HMR 3647 in comparison to oral cefuroxime axetil for the treatment of acute exacerbation of chronic bronchitis in adults. Cefuroxime axetil (Ceftin®) is an antibiotic approved by the Food and Drug Administration for the treatment of acute exacerbation of chronic bronchitis in adults.

If you successfully meet study entry criteria, and agree to participate in this study, you will be randomly assigned (similar to picking numbers out of a hat) to receive, either HMR 3647 800 mg once a day plus placebo once a day for 5 days, followed by placebo twice a day for 5 days; or cefuroxime axetil 500 mg twice a day for 10 days. Neither you nor your doctor or other study personnel will know which medication you have been assigned, however, in the event of an emergency, this information will be made available to your doctor.

Duration of the study: Your participation in the study will be approximately 6 weeks.

Procedures to be followed during the study: A total of approximately 510 subjects will take part in this multicenter, multinational study. If you are selected for inclusion in the study and if you decide to participate, you will be required to make five study visits.

Pretherapy/Entry Visit (Day 1): Before starting the treatment, you will be required to give your medical history, complete a physical examination including vital signs (temperature, blood pressure, and heart rate), chest x-ray, an ECG (electrocardiogram), and an assessment of your infection related signs and symptoms. In addition, you must give a urine sample for urinalysis and a pregnancy test (if applicable). Blood samples will be collected to determine the amount of HMR 3647 in your bloodstream, to determine if there is bacteria in your blood, and for chemistry and hematology laboratory tests. A blood sample will also be collected for a blood pregnancy test (if applicable) to determine that you have not recently become pregnant. You will be asked to provide a sputum sample to determine if you have an infection as the cause of your acute exacerbation of chronic

bronchitis, and if so, what type of bacteria may be causing your infection. A peak expiratory flow rate will be obtained.

On-therapy/Visit 2 (Day 3 - 5): Vital signs, an ECG, an assessment of your infection related signs and symptoms and a peak expiratory flow rate will be obtained. You will also be asked to give a blood and urine sample for laboratory tests. In addition, you will be asked to provide a blood sample to determine the amount of HMR 3647 in your bloodstream. If you are not feeling better, a new antibiotic treatment may be considered necessary by your doctor and you may be asked to have a chest x-ray, give a sputum and/or blood sample to determine the status of your infection.

End of therapy/Visit 3 (Day 11 - 13): A physical examination, vital signs, an ECG, an assessment of your infection related signs and symptoms, and a peak expiratory flow rate will be obtained. You will also be asked to give a blood and urine sample for laboratory tests. In addition, you will be asked to provide a blood sample to determine the amount of HMR 3647 in your bloodstream. If you are not feeling better, a new antibiotic treatment may be considered necessary by your doctor and you may be asked to have a chest x-ray, give a sputum and/or blood sample to determine the status of your infection.

Post therapy/Test of cure/Visit 4 (Day 17 - 24): A physical examination including vital signs, an ECG, an assessment of your infection related signs and symptoms, and a peak expiratory flow rate will be obtained. You may be asked to have an additional chest x-ray, give a urine sample for urinalysis and a blood sample for chemistry and hematology lab tests. You will also be required to give a blood sample for a pregnancy test (if applicable) to make sure you have not become pregnant during the study. You will also need to give a blood sample and/or sputum sample (if possible) to determine if you still have an infection. An ECG may also be repeated if your investigator thinks it is warranted or necessary.

Late post therapy/ Visit 5 (Day 31 - 38): This visit will consist of a physical examination including vital signs, an assessment of your infection related signs and symptoms, and a peak expiratory flow rate. A blood, urine or sputum sample may be collected for laboratory testing, if clinically warranted at this visit. A serum pregnancy test may be done if not collected at Visit 4. In addition, an ECG may be performed at this visit.

Possible hazards, risks and discomforts of participating in the study: Side effects for HMR 3647 include: nausea, vomiting, diarrhea, gas, headache, dizziness, tiredness, impaired concentration, abnormal vision, drowsiness, abnormal taste, dry mouth, mouth sores, skin eruptions and potential ECG abnormalities. Complete knowledge of the side effects or associated adverse reactions for HMR 3647 is not yet known.

The other medication which you may be assigned is cefuroxime axetil. The most frequent adverse effects seen with the administration of cefuroxime axetil include diarrhea and loose stools, nausea and vomiting, increased liver enzymes and increased eosinophils in the blood.

Other than possible discomfort (temporary pain, swelling, bruising, and rarely local infection) caused by the collection of blood samples, no other side effects are anticipated from actual study procedures. It is anticipated that approximately up to 240 ml (8 ounces) of blood will be collected for laboratory tests during the entire study.

Information for women of childbearing potential: The safety of HMR 3647A has not been established during pregnancy or nursing. Therefore, the study drug used in this study may have unforeseen risks to you or to your unborn child should you become pregnant while participating in this study. If you are a woman who is breast feeding, pregnant, or wanting to become pregnant during the course of the trial, you may not enter this study. If you have not been surgically sterilized or post-menopausal for at least one year, you must have had a normal menstrual flow within one month before study entry, have a negative pregnancy test immediately before study entry and agree to use an accepted method of contraceptive (i.e., oral contraceptive with a barrier method, spermicide and barrier method, or IUD). You must also agree to use the same method throughout the study. If you become pregnant during the study, you must stop taking the study medications immediately and contact the investigator. You may be followed to determine the outcome of your pregnancy.

Benefits of the Study: Neither the investigator nor the drug sponsor (Hoechst Marion Roussel, Inc.) guarantee health benefits to you from participation in this study. While you are participating in this study, you will receive the study drug, laboratory tests and examinations required by the study free of charge.

Alternative methods of Treatment: Your doctor may prescribe other medications for your treatment. Some of these may include Erythromycin, Ceftin®, Bactrim®, Biaxin®, Zithromax®, or Levaquin®. Your doctor can discuss these or other available treatments with you.

For the duration of the study, you must notify the investigator of any other medical treatments that may be necessary for you to undergo.

Subject Rights and Study Withdrawal: Participation in this study is entirely voluntary; you are not obliged to take part. Your treatment and the attitude of your doctor towards you will not be affected should you decide not to take part in this study. Refusal to participate will not affect any benefits to which you are otherwise entitled. If you decide to take part, you will need to sign to say that you have given your consent to participate. If you agree to participate, you may nevertheless withdraw from the study at any time, although for your own safety it is advisable to tell the investigator if you intend to do this.

Your participation may be terminated at any time by the investigator, the sponsor or the FDA. This could happen if you experience serious, unforeseen side effects, if you do not follow the study schedule, or there is a change in your medical condition. In any case, you will neither be penalized, nor lose any benefits to which you are otherwise entitled.

The personal information obtained about you during the course of this study will remain confidential; in recording the results of the study, you will be referred to only by a code number and initials.

For the duration of the study, you must notify the investigator of any other medical treatments that may be necessary for you to undergo.

In the event that you experience any adverse reaction to the investigational drug during the course of this study, you should immediately contact the investigator (for name and telephone number see below).

Reimbursement for reasonable medical expenses associated with the treatment of adverse reactions to the investigational drug during the study will be provided by the sponsor, if in the opinion of the

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investigator and the sponsor, the reaction was caused by the proper use of the drug in accordance with the terms of the study. No other compensation will be made available from the sponsor.

You will be given a copy of this informed consent document and may ask for additional information, at any time during the study, from

_____ (*insert name and telephone number of investigator*).

You may also contact _____ (*insert name and telephone number*) if you have questions about your rights as a research subject.

Subject number: _____

1. I have read the informed consent document for this trial. I have received an explanation of the nature, purpose, duration, and foreseeable effects and risks of the trial and what I will be expected to do. My questions have been answered satisfactorily.
2. I agree to take part in this trial. I agree to cooperate fully with the investigator and will contact the investigator immediately if I suffer any unexpected or unusual symptoms during the trial. For the duration of the study, I will notify the investigator of any other medical treatments that may be necessary for me to undergo.
3. I have informed the investigator of all my previous or present illnesses and medication and of any consultation that I have had with my doctor in the past few months.
4. I have further informed the investigator of any participation by me in other clinical studies in the past year.
5. I am aware that if I do not cooperate fully with the investigator's requests and directions, I may harm myself by participating in the study.
6. I understand that my participation in the trial is voluntary and that I may refuse to participate or may withdraw from the trial at any time, without penalty or loss of benefits to which I am otherwise entitled. I further understand that any information that becomes available during the course of the study that may affect my willingness to take part will be disclosed to me as soon as practicable.
7. I agree that results of the study may be passed on to the appropriate authorities, to the sponsor, and to the manufacturer of the drug under study. My name and address will be kept confidential.
8. Representatives of the sponsor, independent ethics committee/institutional review board, or local or foreign regulatory authorities may wish to examine my medical records to verify the information collected. By signing this document, I give permission for this review of my records.

Last name: _____
(block letters)

First name: _____
(block letters)

Signature: _____

Date: _____
(to be completed by subject
at time of consent)

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Investigator/Sub-investigator

I confirm that I have personally explained the nature, purpose, duration, and foreseeable effects and risks of the trial to the subject named above.

Last name: _____ **First name:** _____
(block letters) (block letters)

Signature: _____ **Date:** _____

Witness

Last name: _____ **First name:** _____
(block letters) (block letters)

Signature: _____ **Date:** _____