

INFORMED CONSENT**A MULTICENTER, DOUBLE-BLIND, ACTIVE-CONTROLLED, TWO-ARM
PARALLEL-GROUP STUDY OF THE EFFICACY AND SAFETY OF ORAL
HMR 3647 800 MG ONCE A DAY FOR 5 DAYS VERSUS ORAL
CLARITHROMYCIN 250 MG TWICE A DAY FOR 10 DAYS IN SUBJECTS WITH
GROUP A β -HEMOLYTIC STREPTOCOCCAL PHARYNGITIS/TONSILLITIS****HMR 3647A/3008**

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 this 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 clarithromycin for the treatment of pharyngitis/tonsillitis caused by a specific type of bacteria (group A β -hemolytic streptococci or GABHS). Clarithromycin (Biaxin®) is an antibiotic approved by the Food and Drug Administration for the treatment of GABHS pharyngitis/tonsillitis.

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 (two 400 mg capsules) once a day for 5 days or clarithromycin 250 mg (one 250 mg capsule) three times a day for 10 days. If you are assigned to receive HMR 3647, one of your study medication doses during the day will be HMR 3647 and the other dose will be placebo (similar to sugar pills) for the first five days. Both doses will be placebo for the remaining five days. The reason for this is to keep the identity of the study medications unknown. 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 5 weeks.

Procedures to be followed during the study: Approximately 400 subjects will take part in this study in the U.S. and Canada. If you are selected for inclusion in the study (not all subjects will be included in the study) and if you decide to participate, you will be required to make five study visits.

Entry/Visit 1: Before starting the treatment, an assessment of infection-related signs and symptoms will be made and your throat will be swabbed for two tests to determine if you have an infection caused by a specific type of bacteria. You will be required to provide your medical history, have a physical examination including measurement of vital signs (temperature, blood pressure, and heart rate) and an ECG (electrocardiogram). In addition, you must give a urine sample for urinalysis including a pregnancy test (if applicable) to determine that you are not pregnant. Blood samples will be collected for laboratory tests (including pregnancy test if applicable).

On-therapy/Visit 2: You will have a physical examination, measurement of vital signs, ECG, an assessment of your infection-related signs and symptoms and a throat swab sample will be collected. You will also be asked to give blood and a 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.

End-of-therapy/Visit 3: You will have measurement of vital signs, ECG and an assessment of your infection-related signs and symptoms. 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 for another throat swab sample to determine the status of your infection.

Posttherapy/Visit 4: You will have a physical examination, measurement of vital signs, an assessment of your infection-related signs and symptoms, and a throat swab sample will be collected. You may be asked to have an ECG, and give a urine sample for urinalysis and a blood sample for laboratory 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.

Late posttherapy/Visit 5: You will have a physical examination, measurement of vital signs, an assessment of your infection-related signs, and a urine sample will be collected for laboratory tests. You may be asked to have an ECG, and throat swab and blood samples for laboratory testing.

Possible hazards, risks and discomforts of participating in the study: Side effects of HMR 3647 include nausea, vomiting, diarrhea, gas, headache, dizziness, tiredness, decreased ability to concentrate, abnormal vision, drowsiness, abnormal taste, dry mouth, mouth sores, skin problems, and possible ECG abnormalities which may indicate a change in how your heart is working. Complete knowledge of the side effects or associated adverse reactions for HMR 3647 is not yet known.

The other medication to which you may be assigned is clarithromycin. The most common side effects seen with the administration of clarithromycin in adults have been diarrhea, nausea, abnormal taste, dyspepsia, abdominal pain/discomfort, and headache. In pediatric subjects, diarrhea, vomiting, abdominal pain, rash, and headache have been the most frequently reported side effects.

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 up to approximately 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 3647 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 medication immediately and contact the investigator. You may be asked by the study doctor to keep in contact with him/her and to report the progress of your pregnancy and the health of your baby after it is born.

Benefits of the Study: Neither the investigator nor the study sponsor (Hoechst Marion Roussel, Inc.) guarantees 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: You do not have to participate in this study to receive treatment for your pharyngitis/tonsillitis. Your doctor may prescribe other medications for your treatment. Some of these may include penicillin, amoxicillin, erythromycin, Biaxin®, Zithromax®, Ceclor®, or Cefitin®. Your doctor may discuss these or other available treatments with you.

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 toward 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.

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 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.

Informed Consent Document
HMR 3647A/3008

July 22, 1998 FINAL

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.

Informed Consent Document
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July 22, 1998 FINAL

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 last 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)

For subjects who are less than 18 years of age

Parent or Legal Guardian

Date

I understand and give my assent to take part in this study.

Subject Signature

Date

Informed Consent Document
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July 22, 1998 FINAL

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:** _____