

Informed Consent Document
HMR3647A/3004

July 15, 1998

INFORMED CONSENT

A multicenter, double-blind, active-controlled, two-arm parallel-group study of the efficacy and safety of HMR 3647 800 mg once a day for 5 days versus penicillin VK 500 mg three times a day for 10 days in subjects with group A β -hemolytic streptococcal pharyngitis/tonsillitis

HMR 3647A/3004

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 him/her 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. I agree that, before final inclusion in the study, laboratory tests will be performed. If any of them are positive, I will not be included in the study.
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 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:** _____

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SUBJECT INFORMATION SHEET

A multicenter, double-blind, active-controlled, two-arm parallel-group study of the efficacy and safety of HMR 3647 800 mg once a day for 5 days versus penicillin VK 500 mg three times a day for 10 days in subjects with group A β -hemolytic streptococcal pharyngitis/tonsillitis

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You have been diagnosed as suffering from a pharyngitis/tonsillitis. This disease is a common upper respiratory tract infection that can be caused by bacterial microorganisms. The most common bacteria responsible for it is a group A beta-hemolytic streptococcus (GABHS). GABHS pharyngitis/tonsillitis is treated with antibiotics available on the market to prevent its complication, rheumatic fever.

We propose you to participate in a trial to evaluate the safety and efficacy of a new antibiotic HMR 3647 in the treatment of GABHS pharyngitis/tonsillitis in comparison with penicillin.

Penicillin is the treatment of choice for GABHS pharyngitis/tonsillitis, except in individuals with histories of penicillin allergy.

HMR 3647 is still not approved by the authorities. It has been shown to be safe in healthy volunteers studies, in which the drug was administered at a dose of 50 to 1200 mg. It is expected to be at least as effective as the common drugs prescribed to treat GABHS pharyngitis/tonsillitis, with a shorter duration of treatment compared to penicillin. It could also represent an alternative treatment in subjects allergic to penicillin.

A total of 320 subjects will take part in this study and two different treatment regimens will be studied. In order to be able to compare both drugs in an unbiased way, neither you nor your doctor will know which drug you will be treated with up to the end of the study (double-blind study).

Subjects treated with HMR 3647 will take 800 mg once a day for 5 days followed by 5 days of placebo. Subjects treated with penicillin will take 500 mg three times a day for 10 days. You will have to take 2 capsules three times a day for 10 days and you will have equal chance of receiving one or the other treatment.

Rare cases of ECG abnormalities were reported with some of the orally administered macrolides, which are one of the commonly prescribed treatment for respiratory tract infections. Since HMR 3647 is a derivative of the same group of antibacterial, an ECG will be taken before the administration of the study drug, as a safety investigation, as described below.

If you decide to take part in this study, your participation will be approximately 36 days and your doctor will see you at 5 visits :

Before the start of the treatment, throat swab specimens will be obtained for a rapid streptococcal antigen detection test and culture, an ECG will be performed and blood and urine samples collected (including a blood and urine pregnancy test for women).

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At Day 3-5 (on-therapy) visit, throat swab specimen, laboratory tests (blood and urine samples) will be repeated. ECG will be repeated if necessary.

After the completion of the treatment (Day 11-13 visit), laboratory tests (blood and urine samples) will be repeated. Throat swab specimen and ECG will be repeated if necessary.

Seventeen (17) to 21 days after your first visit, throat swab specimen and serum pregnancy test (in women) will be repeated. Laboratory tests (blood and urine) will be repeated if not done at the previous visit or if judged necessary by your doctor.

Thirty-one (31) to 36 days after your first visit, throat swab specimen and urine samples will be collected. Blood samples for laboratory and pregnancy tests will be repeated if judged necessary by your doctor.

At each visit you will undergo a physical examination (except at visit 3) and vital signs measurements will be taken.

Adverse reactions to be potentially anticipated with HMR 3647 are gastrointestinal effects (nausea, vomiting, abdominal pain, diarrhea), increase in hepatic enzymes and, rarely, allergic reactions. Adverse reactions to be potentially anticipated with penicillin are gastrointestinal effects (nausea, soft stools and rarely diarrhea associated to *Cl. difficile*), skin reactions (rash and sometimes urticaria) and eosinophilia. Rare anaphylactic reactions have been reported.

If you are a woman, it is requested that you avoid becoming pregnant during your participation in the study. An additional method of contraception must be used (spermicide and barrier methods or another accepted method of contraception), even if you are taking oral contraceptive. In the case you suspect that you are pregnant or if you are not using a contraceptive method, you must inform your doctor immediately and you will be, for your own safety, withdrawn from study medication. If you become pregnant you will have to be followed until the end of the pregnancy to assess the effects of the drug.

This antibiotic is not yet on the market, and your doctor will not be able to prescribe it after the completion of the treatment. However, your doctor will prescribe you the appropriate available treatment as judged necessary.

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 a document 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. Sponsor representatives or mandated by the sponsor, regulatory authorities, ethics committee/institutional review board will be granted direct access to your original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality. Your identity will remain confidential even if the results of the trial are reported publicly.

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You or your legally authorized representative will be informed in a timely manner if information becomes available that may be relevant to your willingness to continue to participate in the trial.

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).

The sponsor has taken out insurance coverage in accordance with the requirements in your country.

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.**