INFORMED CONSENT FORM

Official title: Efficacy and mechanism of action of methenamine hippurate (Hiprex™) in the management of recurrent urinary tract infections in women

NCT number: NCT04709601

IRB Approved Document date: 11-09-22

Title of Study: Efficacy and Mechanism of Action of Methenamine Hippurate (Hiprex™) in the Management of Recurrent Urinary Tract Infections in Women

Consent to be part of a Research Study
To be conducted at
The University of Texas Southwestern Medical Center

Key Information about this Study

The purpose of this study is to examine the effectiveness of taking Hiprex to prevent recurrent UTIs (urinary tract infections) in women. The information we will learn from this study will help us determine who may benefit from Hiprex and how to properly prescribe the medication.

Participants in this study will be prescribed a daily treatment with Hiprex to take for a year. During the initial and follow-up visits, urine samples will be collected. Participants will also be asked to fill out a questionnaire regarding symptoms related to UTIs and any possible side-effects of Hiprex.

Hiprex has been around for over a decade now and has a very good tolerance profile. The risk in taking Hiprex is minimal, but side-effects like itching, rash, nausea, and vomiting have been reported.

Information about this form

You may be eligible to take part in a research study. This form gives you important information about the study.

Please take time to review this information carefully. You should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or a doctor) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

Please tell the researchers or study staff if you are taking part in another research study.

Your doctor is a research investigator in this study. He is interested in both your medical care and the conduct of this research study. At any time, you may discuss your care with another doctor who is not part of this research study. You do not have to take part in any research study offered by your doctor.

Voluntary Participation - You do not have to participate if you don't want to. You may also leave the study at any time. If you decide to stop taking part in this research study, it will not affect your relationship with the UT Southwestern staff or doctors. Whether you participate or not will have no effect on your legal rights or the quality of your health care.

If you are a medical student, fellow, faculty, or staff at the Medical Center, your status will not be affected in any way.

General Information – "Who is conducting this research?"

Principal Investigator

The Principal Investigator (PI) is the researcher directing this study; the PI is responsible for protecting your rights, safety and welfare as a participant in the research. The PI for this study is Dr. Philippe Zimmern, MD, Department of Urology at the University of Texas Southwestern Medical Center.

Purpose – "Why is this study being done?"

UTIs are the most common bacterial infection in women. They can lead to bothersome symptoms, such as burning with urination, but can also develop to more serious complications like multi-organ failure and death. Typical treatment involves a short course of antibiotics; however, with recurrent UTIs, repeated exposure to antibiotics can lead to side-effects from the antibiotics used as well as contribute to antibiotic resistance amongst bacteria. Hiprex is a medication that is prescribed for the prevention of recurrent UTIs. Despite its popularity, little is known on how it is metabolized in the body and how it functions in the urine. Thus, the purpose of this study is to analyze the urine of women taking Hiprex to measure the concentration of the byproducts of Hiprex and to determine if the concentration is adequate to kill the bacteria, thus reducing the rate of recurrent UTIs.

You are asked to participate in this research study of Hiprex in order to help the researchers learn how Hiprex functions in the body to stop the bacterial growth that leads to a recurrent UTI.

Information about Study Participants – "Who is participating in this research?"

You are being asked to be a participant in this study because you have recurrent UTIs and are willing to take Hiprex to prevent them.

How many people are expected to take part in this study?
This study will enroll approximately 100 participants.

Information about Study Procedures – "What will be done if you decide to be in the research?"

While you are taking part in this study, you will be asked to attend 4 visits total with the researchers or study staff over the course of a year. In order to reach an appropriate low urinary pH level and be able to continue on with the study, you may have to modify your diet with the help of a dietician and maintain it throughout the course of the study.

Study Procedures - as a participant, you will undergo the following procedures:

Initial visit (V1):
If you have previously been on Hiprex or another methenamine-containing substance, you will be asked about medication history, including the length of time on the medication, the dosage and any changes to dosage, and side-effects experienced while taking the medication.

A 3 day diary with recordings of urine pH before each meal and before bed will be obtained to document if you have consistent low urine pH (<6), a critical condition for methenamine conversion to formaldehyde.

You will be prescribed Hiprex 1 gm to be taken twice a day for a year. Urine samples will be obtained before the first dose to determine if you currently have a UTI. If there are no bacteria present in your urine, you will start the first dose of Hiprex. If you do have a UTI, you will be treated with a course of culture-based antibiotics and will start your first dose of Hiprex when the urine is clear of bacteria. The urine samples will be taken to the lab at UTD and analyzed for formaldehyde and methenamine concentrations (breakdown products of Hiprex believed to have a role in killing bacteria in the urine) and urine pH. The initial visit may take up to thirty minutes to complete.

Follow-up visits (V2-V7):

You will be asked to return to clinic for 3 follow-up visits: 3 months (V2), 6 months (V3), and 12 months (V4) after starting Hiprex. This research visit timing corresponds to standard-of-care clinic visits include 3 months, 6 months, and 12 months. 3 months, 6 months and 12 months represent additional visits to ensure drug compliance and assess the continued effectiveness of Hiprex in the urine. These three visits (V2, V3, and V4) are standard-of-care and will not be charged to your insurance. The main reason for these extra visits is that we do not want patients to take Hiprex for a long time if there is no detectable presence of the breakdown products responsible for bacterial elimination in their urine orthe effect of Hiprex is no longer sustained because of urinary pH changes. This explains why these additional visits were built in this protocol.

In addition, laboratory findings from these visits could lead to potential dose adjustments and/or diet modifications if a more acid pH was desirable.

Could your participation end early? There are several reasons why the researchers may need to end your participation in the study (early withdrawal). Some reasons are:

- The researcher believes that it is not in your best interest to stay in the study, such as if you experience side-effects of taking Hiprex or if urinary pH is unable to reach appropriately low levels to benefit from Hiprex despite diet modification or increase in Hiprex dosage.
- You become ineligible to participate.
- Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- You do not follow instructions from the researchers.
- The study is stopped.

The researchers will discuss your options for medical care when your participation in this study ends.

Risks – "What are the risks of participation in the research?"

Risks from the specific research procedures (drug(s), interventions, or procedures)
There are risks to taking part in this research study. Although minimal, you could have side effects from taking Hiprex and have to come off the study for that reason.

Side effects from this study will usually go away soon after you stop taking Hiprex. In very rare cases, side effects can be long lasting or may never go away.

Everyone taking part in the study will be watched carefully for any side effects. However, the study doctors don't know all the side effects that may happen. Be sure to tell your study doctor immediately, about any side effect that you have while taking part in the study.

The following section will describe the risks related to your participation in this research study. You should talk to your study doctor about any side effects or other problems that you have while taking part in the study.

Side effects can range from mild to serious. Serious side effects are those that may require hospitalization, are life threatening or fatal (could cause death). The frequency that people experience a certain side effect can range from many (likely), few (less likely) or only one or two (rarely).

Risks and side effects related to Hiprex are listed. From the review of the literature, of 100 people taking Hiprex, approximately 4 may experience one of the following side effects:

- Itching
- Skin rash

- Indigestion
- Nausea
- Vomiting

For more information about risks and side effects, ask one of the researchers or study staff.

We will tell you about any significant new findings which develop during the course of this research which may relate to your willingness to continue taking part.

Are there risks related to withdrawing from the study?
If you decide to withdraw from this study early, please discuss your decision with the principal investigator. The researcher may ask you to complete study withdrawal procedures at a final study visit. This visit includes providing a reason for withdrawing early and filling out a final questionnaire regarding symptoms. There is no risk to you if you do not complete the final withdrawal procedures and you can choose not to participate in them.

Are there risks if you also participate in other research studies?
Being in more than one research study at the same time may increase the risk to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers.

What if a research-related injury occurs?
The researchers have taken steps to minimize the known or expected risks. However, you may still experience problems or side effects, even though the researchers are careful to avoid them. In the event of a research-related injury or if you experience an adverse reaction, please immediately contact your study doctor. See the section "Contact Information" for phone numbers and additional information. You may also need to tell your regular doctors.

If you are injured or made sick from taking part in this research study, medical care will be provided. This care may be billed to you or your insurance. Depending on the circumstances, this care may be provided at no cost to you. We have no plans to give you money if you are injured. The investigator can provide you with more information.

If you sign this form, you do not give up your right to seek additional compensation if you are harmed as a result of being in this study.

Benefits – "How could you or others benefit from your taking part in this study?"

The possible benefit of your participating in this study is a potential reduction in the frequency and severity of recurrent UTIs over time as well as confirmation that the dosage of Hiprex prescribed is adequate or conversely needs adjustment. There is no guarantee or promise that you will receive any benefit from this study in the short or long-term but that is the reason the study is undertaken because Hiprex is commonly prescribed, has good reputation, but no one thus far has tested the urine findings to confirm the presence of its active metabolites (breakdown products) where it is expected to work, namely inside your bladder to kill existing harmful bacteria.

We hope the information learned from this study will benefit other people with similar conditions in the future. Faced with a situation of increasing resistance and allergies to antibiotics, Hiprex stands out as a non-antibiotic alternative.

Alternative procedures or course of treatment – "What other options are there to participation in this study?"

There are other options available to you. Your other choices may include:

- Trying lifestyle adjustments, such as drinking more fluids and proper hygiene
- Taking Hiprex without participating in the study
- Receiving no treatment
- A variety of antibiotic therapies or other treatments directed at curbing recurrence of UTIs

Payments – Will there be any payments for participation?

There will be no payment for this study.

Costs – Will taking part in this study cost anything?

You or your health insurance company will be responsible for the cost of Hiprex and for the cost of treatments and procedures that would be done whether or not you took part in this study, such as antibiotics to treat a UTI. It is important to understand that some insurance companies do not cover some costs (for example, approved drugs used in a way different from the package instructions). If your insurance company does not cover these treatments or procedures, you will be required to pay for them. Ask the researchers if you have any questions about what it will cost you to take part in this study (for example bills, fees, or other costs related to the research).

Confidentiality – How will your records be kept confidential?

Information we learn about you in this study will be handled in a confidential manner, within the limits of the law. If we publish the results of the study in a scientific journal or book, we will not identify you. The Institutional Review Board and other groups that have the responsibility of monitoring research may want to see study records which identify you as a subject in this study.

How will my information and/or samples be used?
Your personal information and/or samples collected during this study will not be used or distributed for future research studies even if the information is de-identified and cannot be linked back to you.

Research policies require that private information about you be protected and this is especially true for your health information. However, the law sometimes allows or requires others to see your information. The information given below describes how your privacy and the confidentiality of your research records will be protected in this study. Medical information collected during this study and the results of any test or procedure that may affect your medical care may be included in your medical record. The information included in your medical record will be available to health care providers and authorized persons including your insurance company.

What is Protected Health Information (PHI)?
Protected Health Information is information about a person's health that includes information that would make it possible to figure out whose it is. According to the law, you have the right to decide who can see your protected health information. If you choose to take part in this study, you will be giving your permission to the investigators and the research study staff (individuals carrying out the study) to see and use your health information for this research study. In carrying out this research, the health information we will see and use about you will include: demographic information like your age, ethnicity, and zip code; your medical history; information that we get from your medical record; information you give us during your participation in the study such as during interviews or from questionnaires; and results from laboratory analysis of urine samples.

We will get this information by looking at your health chart at UT Southwestern.

How will your PHI be shared?
Because this is a research study, we will be unable to keep your PHI completely confidential. We may share your health information with people and groups involved in overseeing this research study including:

- The Sponsor, University of Texas at Dallas, funding the study. The sponsor includes any people, entities, groups or companies working for or with the sponsor or owned by the sponsor. The sponsor will receive written reports about your participation in the research. The sponsor may look at your health information to assure the quality of the information used in the research.
- The following collaborators at other institutions that are involved with the study: Dr. Lawrence Retizer at UTD.
- The members of the local research team.
- The Institutional Review Board, Human Research Protection Program Office and the Compliance Office of the University of Texas Southwestern Medical Center, and other groups that oversee how research studies are carried out.
- The Research offices at the University of Texas Southwestern Medical Center
- the Food and Drug Administration (FDA) and other U.S. and international governmental regulatory agencies involved in overseeing drug or device research.
- Representatives of domestic and foreign governmental and regulatory agencies may be granted direct access to your health information for oversight, compliance activities, and determination of approval for new medicines, devices, or procedures.

If you decide to participate in this study, you will be giving your permission for the groups named above, to collect, use and share your health information. If you choose not to let these groups collect, use and share your health information as explained above, you will not be able to participate in the research study.

Parts of your PHI may be photocopied and sent to a central location or it may be transmitted electronically, such as by e-mail or fax. The groups receiving your health information may not be obligated to keep it private. They may pass information on to other groups or individuals not named here.

How will your PHI be protected?
In an effort to protect your privacy, the study staff will use code numbers instead of your name, to identify your health information. Initials and numbers will be used on any photocopies of your study records, and other study materials containing health information that are sent outside of the urology clinic for review or testing. If the results of this study are reported in medical journals or at meetings, you will not be identified.

Do you have to allow the use of your health information?
You do not have to allow (authorize) the researchers and other groups to see and share your health information. If you choose not to let the researchers and other groups use your health information, there will be no penalties but you will not be allowed to participate in the study.

After you enroll in this study, you may ask the researchers to stop using your health information at any time. However, you need to say this in writing and send your letter to Dr. Philippe Zimmern at 4th floor of West Campus Building 3 (2001 Inwood Rd, Dallas TX 75390). If you tell the researchers to stop using your health information, your participation in the study will end and the study staff will stop collecting new health information from you and about you for this study. However, the study staff will continue to use the health information collected up to the time they receive your letter asking them to stop.

Can you ask to see the PHI that is collected about you for this study?

The federal rules say that you can see the health information that we collect about you and use in this study. Contact the study staff if you have a need to review your PHI collected for this study.
You will only have access to your PHI until the study is complete.

How long will your PHI be used?
By signing this form, you agree to let us use and disclose your health information for purposes of the study until the end of the study. This permission to use your personal health information expires when the research ends and all required study monitoring is over.

Contact Information – Who can you contact if you have questions, concerns, comments or complaints?

If you have questions now, feel free to ask us. If you have additional questions, concerns, comments or complaints later or you wish to report a problem which may be related to this study you can reach the study team at 214-645-8787 during normal business hours. After business hours or on weekends you can call 214-645-8765.

The University of Texas Southwestern Medical Center Human Research Protection Program (HRPP) oversees research on human subjects. HRPP and Institutional Review Board (IRB) representatives will answer any questions about your rights as a research subject, and take any concerns, comments or complaints you may wish to offer. You can contact the HRPP by calling the office at 214-648-3060.

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Research Consent & Authorization Signature Section

If you agree to participate in this research and agree to the use of your protected health information in this research, sign this section. You will be given a copy of this form to keep. You do not waive any of your legal rights by signing this form.

SIGN THIS FORM ONLY IF THE FOLLOWING STATEMENTS ARE TRUE:

- You have read (or been read) the information provided above.
- Your questions have been answered to your satisfaction about the research and about the collection, use and sharing of your protected health information.
- You have freely decided to participate in this research or you are voluntarily giving your consent for another person to participate in this study because you believe this person would want to take part if able to make the decision and you believe it is in this person's best interest.
- You understand that a copy of this signed consent document, information about this study, and the results of any test or procedure that may affect your medical care, may be included in your medical record. Information in your medical record will be available to health care providers and authorized persons including your insurance company.
- You authorize the collection, use and sharing of your protected health information (another person's protected health information) as described in this form.

Adult Signature Section

Printed Name of Participant	Signature of Participant	Date	Time AM PM

Printed Name of Person Obtaining Consent	Signature of Person Obtaining Consent	Date	Time AM PM

Blind or Illiterate Signature Section *At the time of consent, also complete this section if consent is obtained from an individual who is unable to read and/or write but can otherwise communicate and/or comprehend English (e.g., blind, physically unable to write, etc.)*

Declaration of witness:

By signing below, I confirm I was present for the entire consent process. The method used for communication (e.g., verbal, written, etc.) with the subject was: _____ .

The specific means (e.g., verbal, written, etc.) by which the subject communicated agreement to participate was: _____.

Printed Name of Witness	Signature of Witness	Date	Time AM PM