URODYNAMIC AND CLINICAL EFFICACY OF MIRABEGRON AMONG NEUROGENIC BLADDER PATIENTS

LETTER OF INFORMATION

INVESTIGATOR
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You have been invited to participate in a research study to determine the effectiveness of the drug Mirabegron in the treatment of neurogenic bladder dysfunction. Since you have symptoms of frequency, urgency and/or urgency incontinence (ie leaking before you reach the toilet) this study is being offered for your consideration. This letter describes the study and your role in it. Please read this letter carefully and ask any questions you have regarding the information it contains.

PURPOSE OF STUDY
The purpose of this study is to examine how Mirabegron works in the treatment of bladder problems among patients with neurologic disease.

Mirabegron is a "beta-3 adrenoreceptor agonist" and it belongs to a new class of medication for the treatment of overactive bladder (OAB). It works by relaxing the bladder muscle and therefore may help to relieve bladder symptoms. It has only recently been available in some countries including Canada (it was first available in Japan in 2011). Mirabegron is approved by Health Canada for sale by prescription. The information from this study is needed to find out whether the medication is effective in treating symptoms of neurogenic bladder dysfunction.

NUMBER OF PEOPLE
Up to 144 participants, both men and women will take part in this study, at multiple Canadian centres. We expect to enroll approximately half of the participants here at St. Joseph's Hospital.

PARTICIPATION
If you agree to participate and are eligible for the study, you will be randomly, by chance (like the flip of a coin) be selected to receive either Mirabegron 25 mg initially then increased to 50mg or Placebo. A placebo is a pill that looks like the real medication but does not contain active ingredient and therefore does not actively treat your condition. If you receive placebo, your condition may go untreated and your symptoms may not improve.

The best way to determine if this treatment is effective is to analyze and compare the results from each group of patients.

The study is double-blind, which means that neither you nor your study doctor will know if you are receiving active medication or placebo. This is to assure an objective evaluation of the study medication effect by you and your study doctor. However, if a medical emergency occurs during the study period that

requires knowledge of the study medication or placebo assigned to you, your study doctor will be able to get this information.

STUDY SCHEDULE

This study will be conducted over a 12-week period with 1 screening visit, plus 3 study visits in the Urology Clinic at St. Joseph's Hospital.

VISIT 1

To determine if you are eligible for this study, after your consent has been documented, details about you will be collected including your age and gender, along with your height and weight. You will be asked detailed questions about your medical history, symptoms, including any medications you may take (prescribed, over-the-counter and herbal medications).

If you are taking any medication that is not allowed to be taken in this study, you may not be able to participate in the study, or you may be asked to stop this medication if you and your doctor agree it is safe to do this.

The study doctor will perform a physical examination. Your blood pressure and heart rate will be measured. If you are female of child bearing potential, a urine pregnancy test will be performed. Your post-void residual (PVR) (volume of urine remaining in your bladder after you have voided) will be measured using a BladderScan/ultrasound (sound waves) probe that is placed on your lower abdomen (belly). You will be asked to complete 4 questionnaires to assess the impact of your bladder problems on your quality of life. These will take ½ to 1 hour to do at Visit 1 and 4.

The screening visit will take a total of approximately 1-2 hours.

VISITS 2-4

You will be scheduled to be seen in the Urology Clinic at St. Joseph's Hospital for study visits 2-4 that will take 2-3 hours each. At visit 3 and 4, you will be required to return all unused study medication (including the empty containers).

A medication and a health review will be done. Your PVR urine volume will be measured. If you are a woman of child bearing potential and the study doctor feels it is necessary, a urine pregnancy test will be done. A urodynamic study will be performed at visits 2 and 4. Urodynamics are a test to see how the bladder behaves. It is common test that is usually done during the assessment of patients with a neurogenic bladder. The test involves placing a small catheter (tube) into the bladder and another catheter into the rectum. The bladder is filled with sterile fluid, and the bladder pressures and volumes are recorded on a computer. The attached study schedule shows the timing and testing done at each of the study visits

PATIENT RESPONSIBILITIES

Use of Contraceptives / Pregnancy

If you are a woman of childbearing potential, you must use a highly effective method of birth control, which includes established use of oral, injected or implanted hormonal methods of contraception, placement of an intrauterine device (IUD) or intrauterine system (IUS). Birth control must be practiced from screening and throughout the study period and for 28 days after the final study drug is taken. Your study doctor will discuss with you what is considered highly effective contraceptives. Any woman who finds that she has become pregnant while taking part in the study should immediately tell her study doctor and must stop study medication. If you do become pregnant during this trial, you will be asked to provide information about your pregnancy and outcome.

Female participants must not donate ova eggs starting at screening and throughout the study period and for 28 days after the final study drug is taken. Women who are nursing (breastfeeding), pregnant or plan on becoming pregnant during the study or for 1 month after, must NOT participate in this study.

Male participants with a partner of childbearing potential must also use an effective contraceptive from screening and continue throughout the study period and for 28 days after the final dose of study drug. All male participants will be provided with Letters of Information to be given to all of their female sexual partner(s) who are of child bearing potential.

Male participants must not donate sperm starting at screening and throughout the study period and for 28 days after the final study drug is taken. Men who are planning on fathering a child during the study or for 28 days after the final study drug is taken, must NOT participate in this study.

Voiding Diary

For 3 days prior to Visits 2 and 4, every time you urinate, you will need to record the following into the diary:

1. Date, time, and volume of urine;
2. Rate the sense of urgency (difficulty in postposing urination);
3. Rate the leakage of urine;
4. Date, time and volume of fluid intake.

Each 24 hour period starts at midnight and ends at midnight the next day. Diary may be kept on consecutive or nonconsecutive days. A new diary will be given to you at visits 1 and 3 and results brought back at visits 2 and 4.

Urinary Pad Test

Prior to visit 2 and 4 you will be asked to collect all incontinence pads used in a 24 hour period. You must use the same brand and type of incontinence pad during each 24 hour period. You will be supplied with a large zip-lock bag in which to store the used pads. The 24 hour period shall start once you awaken to start the day, and remove your overnight pad. All pads used during the day, night, and the first pad the next morning will be sealed in the zip lock bag. Mark the time and date when you begin and complete the test. An empty unused pad will be returned in a separate bag. A new bag will be given to you at visit 3 and the bag with any used pads must be brought back at visit 4. If you do not regularly use pads, we will provide a pad for you to wear for the 24hr period.

Study Medication

You will have to take 1 dose of study drug, each day, at the same time each day. The study drug is to be swallowed whole, not chewed.

Other Medications, Treatments and Concerns

If you are taking other medication for bladder dysfunction such as anticholinergic medication, you must let your study doctor know if you make any changes to the dose of this medication, or if you stop taking it. You must consult with your study doctor before making any changes, including starting any new medications (this includes over-the-counter medications as well as medications you received on prescription) or considering any procedures or surgeries for the bladder during the study. You must let the study nurse know about any change in your regular medications.

Throughout the study, you must let the study doctor know of any illnesses, complaint or abnormalities that you experience, whether or not you think it may be related to the study.

RISKS

As with all medications, Mirabegron can cause side effects. The possible common side effects are: increased blood pressure (7.5-11.3%), common cold symptoms (3.5-3.9%), urinary tract infection (2.9-4.2%) and headache (2.1-3.2%). More uncommon side effects can include: skin rash (hives) (<1%), hypersensitivity (swelling of eyelids, difficulty breathing) (<1%), urinary retention (the inability to empty your bladder) (<1%), heart palpitations (<1%), constipation (1.6%), diarrhea (1.2-1.5%), upper respiratory tract infection (1.5-2.1%), fatigue (1.2-1.4%) and body aches (1.3-1.6%), dizziness (2.6-2.7%), dry eyes (0.49%), blurred vision (0.49%) and abdominal pain (0.6-1.4%). Overall this medication is well tolerated. There may be unknown risks associated with the use of this medication, including the unknown effect of long term use and cancer risk, and/or interactions with other medications. The effect of Mirabegron on sperm, ovum, and pregnancy is unknown.

There are no side effects associated with placebo however, without active medication you may not experience an improvement in your bladder symptoms.

The risks associated with the urodynamic assessment are minimal. Some may experience discomfort during the insertion of the catheters. There is a risk of a urinary tract infection. There may some mild burning with urination after the test. The urine may be stained with blood for a few days. Patients with certain types of spinal cord injuries are at risk of having a sudden onset of high blood pressure, flushing of the face, slow heart rate, nausea, and sweating above the level of the injury. This is known as autonomic dysreflexia, and if this occurs the urodynamic study is stopped and the bladder is drained. Your symptoms will usually resolve at this point.

There may be risks or side effects that are unexpected or unknown at this time.

BENEFITS

The medicine used in this study may help with your bladder symptoms. However, it cannot be guaranteed that you will benefit personally from the study medication. The information obtained from this study may help to treat future patients.

STANDARD OF CARE/ALTERNATIVE TREATMENTS

The standard of care for patients with neurogenic bladder symptoms includes a number of alternative treatments that are available, including other medications, and surgery. If your symptoms remain unchanged during the study you may consider an alternate treatment. If you have any questions about these alternatives you should ask your study doctor for additional information.

CONFIDENTIALITY

Your personal physician may be informed if you agree that you are participating in the study.

Representatives of regulatory authorities (such as Health Canada, the Ethics board , may inspect the study files and your medical records to ensure that the results of the study have been properly recorded. Only study related medical records will be looked at.

The study doctor will keep any personal health information about you in a secure and confidential location for a minimum of 25 years as required by Canadian law. A list linking your study number with your name will be kept by the study doctor in a secure place, separate from your study file.Appropriate precautions will be taken to maintain confidentiality of your medical records and personal information. The inclusion of

your initials, gender and age may allow someone to link the data and identify you. While we will do our best to protect your information there is no guarantee that we will be able to do so.

Your personal information will not be shared with others unless disclosure is required by law, for example, if a court of law orders the disclosure.

The results of this research may be published in scientific journals or presented at medical meetings, but your identity will not be disclosed in such publications or presentations.

OTHER INFORMATION

The urine samples collected from female patients will be used only for determining pregnancy status for the purposes of this study.

VOLUNTARY PARTICIPATION/WITHDRAWAL

Participation in this study is voluntary. You may refuse to participate, refuse to answer any questions or withdraw from the study at any time with no effect on your future care. To protect the integrity of the study, you will not be able to withdraw your data from the study after your data has been sent for analysis. If you withdraw from the study, you will be asked to consider coming for a follow-up visit, if possible, 2 weeks later. You may also be withdrawn from this study without your permission, if, in the opinion of the investigator, further participation will not be in your best interest.

During the course of the research project, new information may become available about the study medication which may influence your willingness to continue to participate in the study. If this happens, your study doctor will tell you about it and discuss with you as to whether or not you wish to continue in the study. If you decide to continue in the study, you will be asked to sign a new consent form.

You do not waive any legal right by signing the consent form. Every precaution will be taken to prevent any injury to you during the study. However, if an injury does occur, you will obtain medical care in the same way that you normally would obtain your medical care.

STUDY COSTS/COMPENSATION

All study tests, examinations and medical care required as part of this study are provided at no cost to you. All study medication will be provided free of charge to you during the study. You will not be paid for your time, or reimbursed for any travel expenses for taking part in this study. However, you will be given a parking pass for the hospital parking garages to cover your parking costs for the study visits.

CONTACTS/MORE INFORMATION

Please keep this Letter of Information and if you have any questions, at any time during this study, contact

Dr. Blayne Welk at 519-646-6367

Urology, St. Joseph's Hospital, 268 Grosvenor Street, London, Ontario, N6A 4V2

or Mary McKibbon, the study nurse working with Dr. Welk at 519-646-6100 ext 65308

In case of emergency, please go to your nearest hospital emergency department.

If you have any questions concerning your rights as a research participant or the conduct of the study you may contact Dr. David Hill, Scientific Director, Lawson Research Institute at 519-646-4716.

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CONSENT FORM

I,_____have read the Letter of Information, have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction.

☐ I consent to have my primary doctor notified of my participation in this study

☐ I Do Not consent to have my primary doctor notified of my participation in this study

_____ _____

Date Signature of Participant

_____

Name of person responsible for obtaining this consent (PRINT)

_____ _____

Date Signature of person responsible for obtaining this consent