

## PATIENT INFORMATION SHEET

### Letrozole v Clomifene Citrate for ovulation

#### Part 1

##### 1. Study title

**A clinical trial comparing letrozole versus clomifene citrate for ovulation induction in infertile women with polycystic ovarian syndrome**

##### 2. Invitation paragraph

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Part 1 tells you the purpose of this study and what will happen to you if you take part.

Part 2 gives you more detailed information about the conduct of the study.

Thank you for reading this.

##### 3. What is the purpose of the study?

Lack of ovulation (egg production), usually referred to as anovulation, is a common cause of infertility in women accounting for about 1 in 4 of all cases. It can arise from a number of causes, of which polycystic ovarian syndrome (PCOS) is by far the commonest and accounts for about 80% of all cases. PCOS is an ovarian disorder characterized by an increased number of ovarian follicles (small cysts) that are tiny fluid-filled sacs that normally contain the eggs. The presence of these cysts in increased numbers is related to the ovary's failure to ovulate. The disorder is associated with irregular menstrual cycles, acne, excess body hair and excess weight.

In infertile women with PCOS, a medicine called *clomifene citrate (CC)* has traditionally been used for more than four decades as the standard treatment to induce ovulation. Although CC is very successful in achieving ovulation (75%), the chance of pregnancy with this treatment is low (only 35%). In addition, the chances of miscarriage (about 30%) and multiple births (about 7%) are increased with CC. The lower pregnancy and higher miscarriage rates during CC treatment have been attributed to the negative effects of CC on the neck and on the lining of the womb.

*Letrozole* is another medicine that has recently been investigated as a potential alternative to CC to induce ovulation in patients with PCOS. It has been used for several years in women for other



indications and its safety is well established. Theoretically, letrozole offers several advantages over CC. In contrast to CC, letrozole, which is as successful as CC in inducing ovulation, does not affect the neck or the lining of the womb. Consequently, letrozole treatment may overcome the above-mentioned problems associated with CC and may therefore increase chances of pregnancy and reduce miscarriages. In addition, letrozole has been shown to reduce chances of multiple pregnancies, a risk well known to occur with CC treatment. However, all these advantages of letrozole remain to be proven.

The aim of this study is to prove or disprove if letrozole is better than CC in generating better pregnancy rates with fewer miscarriages and fewer multiple pregnancies.

#### **4. Why have I been chosen?**

You have a condition called polycystic ovarian syndrome and you are having difficulty getting pregnant. In this study we hope to see if giving one medication is better than another in helping women to achieve a successful pregnancy. We hope that 236 patients will join the study to allow us to reach valid statistical evidence.

#### **5. Do I have to take part?**

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect in any way the standard of care you receive.

#### **6. What will happen to me if I take part?**

This study is a randomised trial, which means you will be put into one of two groups using a randomisation method i.e. you will have an equal chance of being in either group. Women in each group will have a different treatment (letrozole or clomifene citrate (CC)) and these will be compared. The trial is double blind, which means that neither you nor your doctor will know which treatment group you are in (although, if your doctor needs to find out he/she can do so). The study is also a cross-over trial, which means that if the first treatment does not work you will change to the other drug after a 6-week break between treatments. This 6-week break is so that the first drug is cleared from your body before starting the new treatment.

The period of time you could expect to be involved in the research varies according to your response to the treatment with a minimum duration of one month (if conception occurs in the first cycle of treatment) up to a maximum of 12 months (6 cycles on each drug). It is expected that only a minority of patients will need the 12-month treatment. The study will be complete if you conceive at any time or if you do not respond to the two treatments. The study is expected to be completed in 3 years.

The treatment will be given as one capsule a day (CC 50 mg or letrozole 2.5 mg) starting from menstrual cycle day 2 to day 6 (i.e. for 5 days). In the first cycle, the response to treatment will be monitored by repeated pelvic ultrasound scans starting on menstrual cycle day 12 and every 2 – 4 days (about 3 scans on average) until ovulation is detected. A blood sample will be taken on menstrual cycle day 21 to measure concentration of progesterone to confirm ovulation. If ovulation is achieved in the first cycle, you will be asked to continue with the same dose until pregnancy is achieved or for a maximum of 6 cycles. No further scanning will be carried out after the first cycle. If ovulation is not achieved in the first cycle, the dose will be increased to two capsules a day (CC 100 mg or letrozole 5 mg) and the treatment will be monitored in the same way as cycle 1. If ovulation is

achieved with two capsules, treatment will continue with this dose for up to a maximum of 6 courses at this higher dose level or until pregnancy is achieved. There may be women who do not ovulate on two capsules or those who ovulate for 6 cycles but do not conceive. These women will change to the other treatment (after a break of 6 weeks) and will follow the same procedures as above.

In some cases, ovulation may stop after an initial good response on a certain dose. If this occurs in two consecutive cycles at any point during your 7-cycle treatment, you will move to the next step as explained above i.e. increase from one to two capsules with follicle tracking, if already on two capsules you will move to the other treatment after a 6-week break; or if already on the second treatment, the study will end.

There will be no extra visits to the clinic above those involved in your standard diagnosis and treatment. You will visit the clinic for an average of three visits (every 2 – 4 days) in the first cycle for follicle tracking, which is a part of your routine care. In each visit you will have an internal scan to look at the growing follicle in your ovary. The scanning takes about 15 - 20 minutes. This may be repeated in up to three other cycles depending on your response to treatment. Apart from these cycles, you will not need scanning in the rest of the cycles. The day 21 blood sample is also a part of your routine care, although the results of the scanning and progesterone measurement will be used for the purpose of the research.

If extra visits to the clinic are necessary for purposes of the Study, reasonable travel expenses incurred by these extra hospital visits will be reimbursed on request.

#### **7. What are the drugs that are being tested?**

1. Letrozole belongs to a group of drugs called aromatase inhibitors, which suppress oestrogen production. It is currently used in breast cancer patients and is not licensed for use in infertility. However, for several years letrozole has been used for ovulation induction in many clinical studies and the results are promising. It is used in a daily dose of 2.5, 5 or 7 mg for 5 days in the early follicular phase (similar to clomifene citrate); although the optimal dose remains unknown. Treatment is usually monitored with serial ovarian scanning (follicle tracking) and measurement of progesterone in the blood on day 21 of the cycle.

2. Clomifene citrate (CC) has been the most widely used drug in infertility for many years and its dose regimens have been well established. It is similar to the female hormone “oestrogen” and is known to suppress the natural oestrogen. It is given for five days in the early follicular phase usually starting on menstrual cycle day 2. The usual starting daily dose of CC is 50 mg. Treatment is monitored as described above. If the patient does not respond to the starting dose, the dose is increased to 100 mg per day in the next cycle. Once ovulation is achieved on a certain dose, treatment is continued with that dose for 6 months or until pregnancy occurs.

#### **8. What are the alternatives for diagnosis or treatment?**

Currently, there is no licensed alternative to clomifene citrate as a first line treatment to induce ovulation in women with PCOS.

#### **9. What are the side effects of any treatment received when taking part?**

1. Letrozole: Side effects of letrozole are not common and include gastrointestinal disturbance, asthenia (fatigue), hot flushes, headache and back pain.

2. Clomifene citrate: The most common side effects of CC are hot flushes, which occur in about 10% of cases. Other less common (less than 5%) side effects include ovarian cyst formation, abdominal discomfort, nausea, vomiting, breast tenderness, headache, intermenstrual spotting, menorrhagia, weight gain, rashes and reversible hair loss. Other rare side effects include dizziness, nervous tension, vertigo, insomnia, depression and visual disturbances (e.g. halos and streaks around light, blurring and scotoma). These visual effects indicate the withdrawal of treatment and disappear in 1 – 2 weeks leaving no permanent eye damage. Ovarian hyperstimulation syndrome (OHSS) is rare with CC treatment affecting <5% of cases and usually occurs in the mild form. It occurs few days after finishing CC tablets and is characterized by some abdominal distension and discomfort, nausea, diarrhoea and ovarian enlargement.

If you suffer any of these side effects or any other symptoms please report them next time we meet. If you have any concern or in case of any emergency please telephone:

Mr Amer: 01332 724667

Dr Shesha: 01332 347141 and ask for Bleep 1117

#### **10. What are the possible disadvantages and risks of taking part?**

The only theoretical disadvantage of taking part in this study is the possibility (50%) of taking letrozole to induce ovulation, the use of which is not supported by enough evidence and is not licensed for use in this indication. However, the safety of this medicine has been well established and its effectiveness may be superior to the standard CC.

#### **11. What are the possible benefits of taking part?**

The potential benefit of taking part in this study is the possibility of receiving a medicine that may give you a higher chance of achieving a successful pregnancy than the standard CC. However, this cannot be guaranteed. The information we get from this study may help us to treat future patients with polycystic ovarian syndrome who want to become pregnant.

#### **12. What happens when the research study stops?**

If you still not pregnant, you will continue to receive treatment as per hospital care. The one drug, clomifene citrate (CC) will be available but not letrozole.

#### **13. What if something goes wrong?**

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

#### **14. Will my taking part in this study be kept confidential?**

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that might leave the hospital will have your name and address removed so that you cannot be recognised.

If you agree to enter the Study, your GP will be notified of your participation. Also, we may notify other medical practitioners not involved in the research who may be treating you.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making a decision.

## **Part 2**

### **1. What if new information becomes available?**

Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw your research doctor will make arrangements for your care to continue. If you decide to continue in the study you may be asked to sign an updated consent form.

Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. The reasons will be explained to you and the arrangements for your care to continue.

### **2. What happens if I do not want to carry on with the study?**

If you do not wish to continue with the study, you are free to withdraw at any time and this will not affect your hospital care.

If you withdraw from the study, with your permission we will use the data collected up to your withdrawal.

### **3. What if there is a problem?**

#### **Complaints**

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (please see contact details at the end of the Patient Information Sheet).

If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the Hospital PALS Office.

#### **Harm**

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Derby Hospitals NHS Foundation Trust but you will have to pay your legal costs. The normal National Health Service complaints mechanism will still be available to you. For non-negligent harm NHS indemnity does not offer no-fault compensation.

### **4. Will my taking part in this study be kept confidential?**

All information that is collected about you during the course of the research will be kept strictly confidential and any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised.

When you agree to enter the Study, with your permission your General Practitioner (GP) will be told of your entry into the Study and will be kept informed of your progress. Also we may notify other medical practitioners not involved in the research who may be treating you.

### **5. What will happen to the results of the research study?**

The results will be published in one of the periodical medical journals. These will also be presented in one of the scientific meetings. However, the published/presented information will not include any identifying information for all the participants. At the end of the study we will notify all the participants of the outcome and as to how obtain a copy of the publication. Participants will also be able to know, on request, which treatment they had received.

#### **6. Who is organising and funding the research?**

The Study will be funded by the NHS Research and Development funds and the co-sponsor is the University of Nottingham. Your doctor is not being paid for including and looking after patients in this Study.

#### **7. Who has reviewed the study?**

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This Study has been reviewed and given favourable opinion by the West Midlands Multi-Centre Research Ethics Committee.

#### **8. Further Information and Contact Details**

Further details about this Study can be obtained from:

Mr S Amer

Associate Professor and Consultant in Obstetrics &Gynaecology

Derby City General Hospital

Tel: 01332 724668 and

Dr Shesha

Research Registrar

Derby City General Hospital

Tel: 01332 340131 and ask for Bleep 1117

#### **Thank you for taking part in this study.**

Please keep this Patient Information Sheet and, if you agree to participate in the Study, a copy of the signed consent form will be given to you to keep.