

PART III: CONSUMER INFORMATION**GONAL-f®**

(follitropin alfa for injection)

This leaflet is part III of a three-part "Product Monograph" published when GONAL-f was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about GONAL-f. Contact your doctor or pharmacist if you have any questions about the drug.

This leaflet contains answers to many questions about infertility and the treatments you are receiving with GONAL-f. Please read this information carefully and discuss any questions or concerns you may have with your doctor.

ABOUT THIS MEDICATIONWhat is GONAL-f?

GONAL-f is follicle-stimulating hormone (FSH) with no urinary proteins, which stimulates oocyte (egg) development in women. GONAL-f is a highly purified recombinant human form of FSH, manufactured using the latest technology with proven effectiveness and safety in clinical studies.

GONAL-f belongs to a group of medicines called "gonadotropins".

What is GONAL-f used for?

GONAL-f is used to stimulate the maturation of follicles in ovulatory patients undergoing Assisted Reproductive Technologies (ART) such as *in vitro* fertilization (IVF). To complete the maturation of follicles, another hormone, hCG (human chorionic gonadotropin), is given.

GONAL-f is also used to stimulate the maturation of follicles in some patients whose menstrual cycle is either irregular or absent. To complete the maturation of follicles another hormone, hCG, is given.

When should GONAL-f not be used?

GONAL-f should **not** be used if you:

- Have high levels of FSH indicating primary ovarian failure
- Have uncontrolled thyroid or adrenal dysfunction
- Are allergic (hypersensitive) or have a history of hypersensitivity to FSH or to any of the other ingredients of GONAL-f
- Are pregnant or breastfeeding
- Have ovarian enlargement or a cyst not due to polycystic ovarian disease (PCO)
- Have a vaginal bleeding of unknown cause
- Have tumours of the ovary, uterus, breast or brain (hypothalamus or pituitary gland)

The medicinal ingredient in GONAL-f:

Follitropin alfa.

The non-medicinal ingredients in GONAL-f:

The non-medicinal ingredients in GONAL-f 75 IU (5.5 µg) single

dose vials are: sucrose, disodium phosphate dihydrate, methionine, Polysorbate 20 and sodium dihydrogen phosphate monohydrate. GONAL-f may also contain O-phosphoric acid and/or sodium hydroxide used for pH adjustment.

The diluent provided for reconstitution is Sterile Water for Injection, Ph.Eur./USP.

What dosage forms of GONAL-f are available?

GONAL-f is available as a lyophilized powder for reconstitution in vials.

GONAL-f is available in 75 IU (5.5 µg) single dose vials.

Each box for the single doses contains a vial of medication (white powder), a pre-filled syringe of sterile water for injection, Ph.Eur./USP (liquid) and a needle for mixing and a needle for injection.

How is GONAL-f administered?

GONAL-f cannot be taken orally because it would be digested in the stomach and for this reason, it must be taken by injection. Due to its high level of purity, GONAL-f is approved for subcutaneous injection (just under the skin), which is easier and less painful than intramuscular injections (in the muscle). In fact, with professional guidance, you can learn to inject yourself, in the comfort and privacy of your own home.

How is GONAL-f different from other treatments?

Over the years, the gonadotropin drugs used in the treatment of infertility have undergone significant changes and improvements. Many other products that are not derived from recombinant technology contain FSH and varying amounts of LH and urinary proteins.

GONAL-f is produced through rDNA technology and consists only of highly purified rFSH.

How long will one treatment cycle last?

This depends on the average follicular response to therapy. Every treatment cycle is individualized and your doctor will need to carefully evaluate how you respond.

WARNINGS AND PRECAUTIONS**General**

To help avoid side effects and ensure proper use, talk to your doctor or pharmacist before you take GONAL-f.

Your fertility should be evaluated before the treatment is started by a doctor experienced in treating fertility disorders.

Porphyria

If you have porphyria or a family history of porphyria, GONAL-f may increase the risk of an acute attack. Tell your doctor immediately if:

- Your skin becomes fragile and easily blistered, especially skin that has been frequently in the sun,

- and/or
- You have stomach, arm or leg pain

In case of the above events your doctor may recommend that you stop treatment.

Overstimulation of the Ovary During FSH Therapy

Ovarian Enlargement

Use of FSH therapy to stimulate follicular development may result in the growth of more than one follicle. This may result in mild to moderate uncomplicated ovarian enlargement which may be accompanied by abdominal distention and/or abdominal pain. It is more commonly seen in women with polycystic ovarian syndrome.

Ovarian Hyperstimulation Syndrome (OHSS)

Treatment increases your risk of developing ovarian hyperstimulation syndrome (OHSS). This is when multiple follicles develop and may become large cysts. In rare cases, severe OHSS may be life-threatening. OHSS may cause fluid build-up in your abdominal and chest areas and can cause blood clots to form. Call your doctor right away if you notice severe abdominal swelling, pain in the stomach area (abdomen), feeling sick (nausea), vomiting, sudden weight gain due to fluid build-up, diarrhea, decreased urine output or trouble breathing. However, if you follow your doctor's instructions for the recommended dose and schedule of administration, the occurrence of OHSS is uncommon. GONAL-f treatment seldom causes significant OHSS unless the medicine used to induce final follicular maturation and ovulation (containing human chorionic gonadotropin or hCG) is administered. In cases where OHSS is developing it is recommended to not give hCG, and women should prevent pregnancy at this time by not having sexual intercourse.

Breathing and Blood Clotting

Serious breathing problems (e.g., lung collapse, extreme shortness of breath and worsening of asthma) have been reported with use of gonadotropin therapy.

Treatment with gonadotropin therapy may increase the risk of having a blood clot (thrombosis) which may or may not be associated with Ovarian Hyperstimulation Syndrome. Blood clots can lead to serious medical conditions, such as blockage in the lungs (pulmonary embolus), blood vessel problems (thrombophlebitis), heart attack, stroke, blockage in the arteries in your arms and legs which may result in a loss of your arm or leg. In rare cases, lung complications and/or blood clots have resulted in death.

Reproductive Issues

Since women with infertility undergoing assisted reproduction, particularly IVF, may have tubal abnormalities, the incidence of ectopic pregnancies (pregnancy in the fallopian tubes) might be increased. Early ultrasound to confirm that a pregnancy is in the uterus is important.

Miscarriages may be higher than in the normal population, but comparable with the rates found in women with fertility problems.

Reports of multiple births have been associated with fertility

treatments. You should discuss the potential risk of multiple births with your doctor before beginning treatment.

The incidence of multiple births with GONAL-f is no different from any other gonadotropin and is dependent upon the protocol used by the clinic. Your doctor will monitor you closely to help minimize the possibility of a multiple pregnancy. The majority of births (about 80%) are single babies. Of those women who do have multiple births, the majority of these are twins. Only very few women conceive 3 or more babies. Even so, neither single nor multiple births can be guaranteed.

There have been reports of ovarian and other reproductive system tumours in women who have had infertility treatment. It is not known if treatment with fertility medicines increase the risk of these tumours in infertile women.

INTERACTIONS WITH THIS MEDICATION

GONAL-f is often used with other medicines to stimulate ovulation (e.g. hCG and LH) which may help the maturation of follicles. If a GnRH agonist or antagonist medicine is also given along with your GONAL-f in your treatment program, you may be told by your doctor to change your dose of GONAL-f. No other significant interactions with other medicines have been reported.

PROPER USE OF THIS MEDICATION

Always take GONAL-f exactly as your doctor has instructed you. You should check with your health care provider if you are unsure.

Recommended Dose

Every treatment is individualized. Your treatment has been carefully designed for you by your doctor. Over the course of your treatment, doses may range between 75 to 450 IU depending on your specific medical condition and your response to the medicine.

Overdose

What should I do if I accidentally inject more than my prescribed amount of GONAL-f?

The effects of an overdose of GONAL-f are unknown. You should contact your doctor for advice if you take more than your prescribed dose of GONAL-f.

Missed dose

What should I do if I forget to take my GONAL-f?

Do not take a double dose to make up for any doses you have missed. Contact your doctor for advice if you forget to take a dose of GONAL-f.

Where should I inject GONAL-f?

The most easily accessible areas for subcutaneous injection are the abdomen and thighs. The absorption of GONAL-f is the same regardless of the injection site selected. You may find the injection is more comfortable if you vary the site each time you

inject GONAL-f.

Below is a diagram with shaded areas demonstrating the recommended subcutaneous injection sites.



HOW TO INJECT GONAL-f

A Step by Step Guide

Understandably, you may be a little apprehensive at first about giving yourself an injection. That is why this information has been produced. Refer to it as necessary and follow each instruction step by step. If you have any questions or concerns that are not addressed here, please consult your clinic.

Every treatment is individualized. Yours has been carefully designed for you by your doctor according to your own specific needs. It is very important that you keep your appointments and follow your doctor's instructions, particularly with regard to the amount and frequency of the medication you are taking. If you have concerns regarding your dosage, consult your doctor. Do not adjust your dosage without being instructed to do so. If you forget or miss an injection, do not panic, but you should call your doctor for advice.

IMPORTANT POINTS TO REMEMBER

Always follow the basic principles of self injection:

- It is recommended that you inject GONAL-f at around the same time each day.
- Use a clean work surface and clean skin as directed.
- Always check expiry date before use. Never use expired GONAL-f.
- Check dosage and instructions for mixing.
- Be sure to use the correct strength and correct amount of diluent.
- Check medication after reconstitution - do not use if medication is cloudy, lumpy or discoloured.
- Alternate injection sites each day.
- Check and record site of injections each day.

If you are unsure about the mixing of the solution, or have difficulty with the injections, call Momentum at 1-800-387-8479 or your clinic immediately.

Please read through the following instructions before you begin, in order to become familiar with self-administration of GONAL-f. If you have been prescribed GONAL-f single dose vials, but the diluent is in a vial, please see your clinic for the specific reconstitution steps.

Please note that µg is pronounced "microgram" and is a unit of measure. 1 gram is equivalent to 1 million micrograms.

1. GETTING READY

- On a clean work surface, lay out everything you will need:
 - GONAL-f mono-dose vial(s) of white powder
 - Diluent in pre-filled syringe
 - One needle for reconstitution (mixing)

- One ½ inch, 25, 27 or 29 gauge needle for injection
- Two alcohol wipes
- Needle disposal container
- If you use your kitchen to prepare the injection, ensure that all medicines and needles are kept well away from food. As for the injection itself, it can be given in any room where you feel comfortable.

2. CLEANSE

- Before you start, wash your hands well with soap and water. It is important that your hands and the items you use be as clean as possible.
- Needles should not touch any surface except inside the vials and alcohol-cleaned skin; keep them capped prior to use.
- Make sure you use a new needle each time you inject to avoid contamination.

3. PREPARE THE PRE-FILLED SYRINGE OF DILUENT

- Carefully twist off the cap at the tip of the barrel of the pre-filled syringe.
- Remove the mixing needle from its package, being careful to keep the protective needle cap in place.
- Carefully twist the mixing needle onto the barrel of the pre-filled syringe until it is tightened.
- Carefully lay the syringe down on a flat, clean, surface.

Reconstitution Volumes

Volumes used for reconstitution should be between 0.5 and 1.0 mL; up to 225 IU (16.5 µg) may be dissolved in 0.5 ml of diluent (Sterile Water for Injection, USP). Following reconstitution, the medication in the vials should be used immediately, and any unused solution should be discarded.

4. MIXING GONAL-f SINGLE DOSE VIAL(S)

- You should have a set number of vials, as prescribed by your doctor, containing GONAL-f (white powder).
- Using your thumb, flip off the plastic cap of the GONAL-f vial.
- Continue to open all vials in this manner, if required.
- Wipe the rubber stopper on the top of the vial with an alcohol wipe.
- Carefully twist the needle cap off the pre-filled syringe labelled "Sterile Water for Injection, USP" prepared in previous step 3.
- Position the needle in a straight, downward position over the marked centre circle of the rubber stopper on the vial of GONAL-f powder.
- Keep the needle in a straight, downward position as you insert it through the centre circle or it may be difficult to depress the plunger.
- Slowly inject the liquid into the vial by pushing the syringe plunger down (volume to be confirmed by your physician). The sterile water and white powder will mix to form a clear liquid.
- Do not shake the vial. If bubbles appear, wait a few moments for the bubbles to settle.
- **DO NOT USE IF SOLUTION APPEARS CLOUDY, LUMPY or DISCOLOURED.** Report this and the lot

number to your doctor.

- When all of the sterile water (diluent) has been injected into the vial, keep the needle in the vial, lift the vial and turn it upside down with the needle pointing toward the ceiling. With the needle tip in the liquid, slowly pull back the plunger until the vial is empty. Be careful not to pull the plunger out of the syringe. Remove the needle from the vial.
- **If you have been prescribed more than one vial of GONAL-f, repeat the points above using the mixed solution in the syringe to dissolve the next vial. Continue in the same manner until you have the prescribed number of powder vials dissolved in the solution.**
- Discard empty vials in the needle disposal container.

5. REMOVE AIR BUBBLES AND CHANGE NEEDLE

- Hold the syringe with the needle pointing upwards and gently flick the syringe if there are any visible air bubbles. The air bubbles will collect at the top of the syringe. If there are no air bubbles, or if there is no air space at the top of the syringe, pull the plunger back to allow an air space.
- Recap the needle and twist to remove; replace with the ½ inch, 25, 27 or 29 gauge injection needle with cap. Lay syringe down on the clean surface.
- Do not worry if you are unable to remove very tiny bubbles; they will do no harm. When you invert the syringe, the air space will be next to the plunger. This space will ensure that all of the medication has been injected. The air will remain in the needle.

6. PREPARE THE INJECTION SITE

- Select the site of injection (e.g. top of thigh, tummy).
- Wipe the chosen area with an alcohol wipe, cleansing an area of approximately 5 cm x 5 cm.
- Lay the used side of the wipe next to your working surface or on the alcohol wipe wrapper.

7. INJECTING THE SOLUTION

- Pick up the syringe and remove the cap from the needle.
- Invert the needle and hold as if throwing a dart.
- With your other hand, gently squeeze the skin together to make a little elevation at the injection site.
- Using a "dart like motion", insert the needle at a 90-degree angle (You need very little force but quick action).
- Once the needle is inserted into the tissue all the way, inject the solution by pushing gently on the plunger with your thumb or index finger of the hand holding the syringe. Take as much time as you need to inject all the solution.
- Immediately withdraw the needle and clean the site with the clean side of the alcohol swab using a circular motion. If there is minor oozing you may need to apply a small amount of pressure for a minute.

8. DISPOSE OF ALL USED ITEMS

- Once you have finished your injection, immediately discard the needles and syringe (without recapping the needle) into the disposal container.
- Take the container to a clinic or pharmacy for proper disposal when the needle disposal container is full or when you have completed your entire treatment.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Are there any side effects with gonadotropin therapy?

Fertility drugs are safe to take with close monitoring by your doctor. As with all medication, there is a potential for side effects.

The following side effects have been reported with the use of GONAL-f during clinical trials and post-market use:

Common and Very Common: may affect 1 to 10 users in 100

- Ovarian cysts
- Mild to moderate ovarian enlargement
- Breast tenderness
- Mild to moderate OHSS
- Mild to severe injection site reaction (such as pain, redness, bruising, swelling and/or irritation)
- Headache
- Stomach pain or bloating
- Feeling sick (nausea), vomiting, diarrhea

Uncommon, Rare and Very Rare: may affect less than 1 to 10 users in 1,000

- Severe OHSS
- Blood clots (thrombosis)
- Difficulty breathing (acute pulmonary distress)
- Worsening of asthma
- Mild to severe allergic reactions (hypersensitivity) such as rash, red skin, hives, swelling of your face with difficulty breathing may occur. These reactions can sometimes be serious.

The greatest concern your doctor will have is ovarian hyperstimulation syndrome (OHSS). To avoid the development of OHSS, your doctor will carefully monitor your response to GONAL-f. Ovarian enlargement, sometimes accompanied by abdominal bloating and pain, may occur in about 20% of women taking gonadotropins. This is generally reversed with cessation of treatment and severe life-threatening cases are rare.

A causal relationship between treatment with fertility drugs and ovarian cancer has not been established.

The following medical events have been reported subsequent to pregnancies resulting from gonadotropin therapy in controlled clinical trials: spontaneous abortion, tubal pregnancy, premature labour, postpartum fever and congenital abnormalities.

None of these events were thought to be drug-related. The incidence is not more than that found in the general population.

This is not a complete list of side effects. If you experience any unusual symptoms or side-effects while taking GONAL-f, you should report them to your doctor or pharmacist immediately. It is also wise to discuss the possibility of side effects with your doctor before you begin treatment.

HOW TO STORE IT

GONAL-f vials of lyophilized powder are stable when stored at or below room temperature (25°C) and protected from light.

Do not freeze.

Do not use the product after the expiry date indicated on the label.

Reconstituted Product

Check medication after reconstitution - do not use if medication is cloudy, lumpy or discoloured.

Following reconstitution, the medication in the vials should be used immediately, and any unused solution should be discarded.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<http://www.hc-sc.gc.ca/dhpmps/medeff/report-declaration/index-eng.php>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained from:

EMD Serono, A Division of EMD Inc., Canada.
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Mississauga ON L5K 2N6

This leaflet was prepared by EMD Serono, A Division of EMD Inc., Canada

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