1. NAME OF THE MEDICINAL PRODUCT

GONAL-f 75 IU (5.5 micrograms), powder and solvent for solution for injection

serono

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 6 micrograms follitropin alfa, recombinant human follicle stimulating hormone (FSH) in order to deliver 5.5 micrograms, equivalent to 75 IU. The reconstituted solution contains 75 IU/ml. Follitropin alfa is produced in genetically engineered Chinese Hamster Ovary (CHO) cells.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.
Appearance of the powder: white lyophilised pellet.
Appearance of the solvent: clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

1) GONAL-f followed by chorionic gonadotrophin (hCG), is recommended for the stimulation of follicular development and ovulation in women with hypothalamic-pituitary dysfunction who present with either oligomenorrhoea or amenorrhoea . These women are classified as WHO group II patients and usually receive clomiphene citrate as primary therapy. They have evidence of endogenous oestrogen production and thus will either spontaneously menstruate or experience withdrawal bleeding after progestagen administration. Polycystic ovarian disease (PCOD) is part of the WHO II classification and is present in the majority of these patients.
2) GONAL-f is indicated for stimulation of multifollicular development in patients undergoing superovulation for assisted reproductive technologies (ART) such as in vitro fertilization (IVF), gamete intra-fallopian transfer (GIFT) and zygote intra-fallopian transfer (ZIFT).
3) GONAL-f is indicated with concomitant human chorionic gonadotrophin (HCG) therapy for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism.

4.2 Posology and method of administration

Treatment with GONAL-f should be initiated under the supervision of a physician experienced in the treatment of fertility problems.

GONAL-f is intended for subcutaneous and intramuscular administration. The powder should be reconstituted immediately prior to the first use with the solvent provided. In order to avoid the injection of large volumes, up to 3 vials of product may be dissolved in 1 ml of solvent.

The dosage recommendations given for GONAL-f are those in use for urinary FSH. Clinical assessment of GONAL-f indicates that its daily doses, regimens of administration, and treatment monitoring procedures should not be different from those currently used for urinary FSH-containing preparations. However, when these doses were used in a clinical study comparing GONAL-f and urinary FSH, GONAL-f was more effective than urinary FSH in terms of a lower total dose and a shorter treatment period needed to achieve pre-ovulatory conditions. Bioequivalence has been demonstrated between equivavalent doses of the monodose presentation and the multidose presentation of GONAL-f. It is advised to adhere to the recommended starting doses indicated below.

Women with hypothalamic – pituitary dysfunction who present with either oligomenorrhoea or amenorrhoea (WHO grupe II):
The object of GONAL-f therapy is to develop a single mature Graafian follicle from which the ovum will be liberated after the administration of hCG.

GONAL-f may be given as a course of daily injections. In menstruating patients treatment should commence within the first 7 days of the menstrual cycle.

Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and/or oestrogen secretion. A commonly used regimen commences at 75-150 IU FSH daily and is increased preferably by 37.5 or 75 IU at 7 or preferably 14 day intervals if necessary, to obtain an adequate, but not excessive, response. The maximal daily dose is usually not higher than 225 IU FSH. If a patient fails to respond adequately after 4 weeks of treatment, that cycle should be abandoned and the patient should recommence treatment at a higher starting dose than in the abandoned cycle.

When an optimal response is obtained, a single injection of 5 000 IU, up to 10 000 IU hCG should be administered 24-48 hours after the last GONAL-f injection. The patient is recommended to have coitus on the day of, and the day following, hCG administration. Alternatively intrauterine insemination (IUI) may be performed.

If an excessive response is obtained, treatment should be stopped and hCG withheld (see warnings). Treatment should recommence in the next cycle at a dosage lower than that of the previous cycle.

Women undergoing ovarian stimulation for multiple follicular development prior to *in vitro* fertilisation or other assisted reproductive technologies:
A commonly used regimen for superovulation involves the administration of 150-225 IU of GONAL-f daily, commencing on days 2 or 3 of the cycle. Treatment is continued until adequate follicular development has been achieved (as assessed by monitoring of serum oestrogen concentrations and/or ultrasound examination), with the dose adjusted according to the patient's response, to usually not higher than 450 IU daily. In general adequate follicular development is achieved on average by the tenth day of treatment (range 5 to 20 days).

A single injection of up to 10 000 IU hCG is administered 24-48 hours after the last GONAL-f injection to induce final follicular maturation.

Down-regulation with a gonadotrophin-releasing hormone (GnRH) agonist is now commonly used in order to suppress the endogenous LH surge and to control tonic levels of LH. In a commonly used protocol, GONAL-f is started approximately 2 weeks after the start of agonist treatment, both being continued until adequate follicular development is achieved. For example, following two weeks of treatment with an agonist, 150-225 IU GONAL-f are administered for the first 7 days. The dose is then adjusted according to the ovarian response.

Overall experience with IVF indicates that in general the treatment success rate remains stable during the first four attempts and gradually declines thereafter.

Men with hypogonadotrophic hypogonadism:
GONAL-f should be given at a dosage of 150 IU three times a week, concomitantly with hCG, for a minimum of 4 months. If after this period, the patient has not responded, the combination treatment may be continued; current clinical experience indicates that treatment for at least 18 months may be necessary to achieve spermatogenesis.

4.3 Contraindications

GONAL-f must not be used in:
- hypersensitivity to follitropin alfa, FSH, or to any of the excipients
- case of tumours of the hypothalamus and pituitary gland

and in women:
- ovarian enlargement or cyst not due to polycystic ovarian disease
- gynaecological haemorrhages of unknown aetiology
- ovarian, uterine or mammary carcinoma

GONAL-f should not be used when an effective response cannot be obtained, such as:
In women:
- primary ovarian failure
- malformations of sexual organs incompatible with pregnancy
- fibroid tumours of the uterus incompatible with pregnancy

In men:
primary testicular insufficiency

4.4 Special warnings and special precautions for use

GONAL-f is a potent gonadotrophic substance capable of causing mild to severe adverse reactions, and should only be used by physicians who are thoroughly familiar with infertility problems and their management.

Gonadotrophin therapy requires a certain time commitment by physicians and supportive health professionals, as well as the availability of appropriate monitoring facilities. In women, safe and effective use of GONAL-f calls for monitoring of ovarian response with ultrasound, alone or preferably in combination with measurement of serum oestradiol levels, on a regular basis. There may be a degree of interpatient variability in response to FSH administration, with a poor response to FSH in some patients. The lowest effective dose in relation to the treatment objective should be used in both men and women.

Self-administration of GONAL-f should only be performed by patients who are well motivated, adequately trained and with access to expert advice. During training of the patient for self administration, special attention should be given to specific instructions for the use of the multidose and/or the monodose presentation(s).

The first injection of GONAL-f should be performed under direct medical supervision.

Treatment in women
Before starting treatment, the couple's infertility should be assessed as appropriate and putative contraindications for pregnancy evaluated. In particular, patients should be evaluated for hypothyroidism, adrenocortical deficiency, hyperprolactinemia and pituitary or hypothalamic tumours, and appropriate specific treatment given.

Patients undergoing stimulation of follicular growth, whether in the frame of a treatment for anovulatory infertility or ART procedures, may experience ovarian enlargement or develop hyperstimulation. Adherence to recommended GONAL-f dosage and regimen of administration, and careful monitoring of therapy will minimise the incidence of such events. Accurate interpretation of the indices of follicle development and maturation require a physician who is experienced in the interpretation of the relevant tests.

In clinical trials, an increase of the ovarian sensitivity to GONAL-f was shown when administered with lutropin alfa. If an FSH dose increase is deemed appropriate, dose adaptation should preferably be at 7-14 day intervals and preferably with 37.5-75 IU increments.

No direct comparison of GONAL-f/LH versus human menopausal gonadotrophin (hMG) has been performed. Comparison with historical data suggests that the ovulation rate obtained with GONAL-f/LH is similar to what can be obtained with hMG.

Ovarian Hyperstimulation Syndrome (OHSS)
OHSS is a medical event distinct from uncomplicated ovarian enlargement. OHSS is a syndrome that can manifest itself with increasing degrees of severity. It comprises marked ovarian enlargement, high serum sex steroids, and an increase in vascular permeability which can result in an accumulation of fluid in the peritoneal, pleural and, rarely, in the pericardial cavities.

The following symptomatology may be observed in severe cases of OHSS: abdominal pain, abdominal distension, severe ovarian enlargement, weight gain, dyspnoea, oliguria and gastrointestinal symptoms including nausea, vomiting and diarrhoea. Clinical evaluation may reveal hypovolaemia, haemoconcentration, electrolyte imbalances, ascites, haemoperitoneum, pleural effusions, hydrothorax, acute pulmonary distress, and thromboembolic events.

Excessive ovarian response to gonadotrophin treatment seldom gives rise to OHSS unless hCG is administered to trigger ovulation. Therefore in cases of ovarian hyperstimulation it is prudent to withhold hCG and advise the patient to refrain from coitus or to use barrier methods for at least 4 days. OHSS may progress rapidly (within 24 hours to several days) to become a serious medical event, therefore patients should be followed for at least two weeks after hCG administration.

To minimise the risk of OHSS or of multiple pregnancy, ultrasound scans as well as oestradiol measurements are recommended. In anovulation the risk of OHSS and multiple pregnancy is increased by a serum oestradiol > 900 pg/ml (3300 pmol/l) and more than 3 follicles of 14 mm or more in diameter. In ART there is an increased risk of OHSS with a serum oestradiol > 3000 pg/ml (11000 pmol/l) and 20 or more follicles of 12 mm or more in diameter. When the oestradiol level is > 5500 pg/ml (20200 pmol/l) and where there are 40 or more follicles in total, it may be necessary to withhold hCG administration.

Adherence to recommended GONAL-f dosage, regimen of administration and careful monitoring of therapy will minimise the incidence of ovarian hyperstimulation and multiple pregnancy (see Sections 4.2 'Posology and method of administration' and 4.8 'Undesirable effects'). In ART, aspiration of all follicles prior to ovulation may reduce the occurrence of hyperstimulation.

OHSS may be more severe and more protracted if pregnancy occurs. Most often, OHSS occurs after hormonal treatment has been discontinued and reaches its maximum at about seven to ten days following treatment. Usually, OHSS resolves spontaneously with the onset of menses.

If severe OHSS occurs, gonadotrophin treatment should be stopped if still ongoing, the patient hospitalised and specific therapy for OHSS started.
This syndrome occurs with higher incidence in patients with polycystic ovarian disease.

Multiple pregnancy
Multiple pregnancy, specially high order, carries an increase risk in adverse maternal and perinatal outcomes.

In patients undergoing ovulation induction with GONAL-f, the incidence of multiple pregnancies is increased as compared with natural conception. The majority of multiple conceptions are twins. To minimise the risk of multiple pregnancy, careful monitoring of ovarian responses recommended.

In patients undergoing ART procedures the risk of multiple pregnancy is related mainly to the number of embryos replaced, their quality and the patient age.

The patients should be advised of the potential risk of multiple births before starting treatment.

Pregnancy wastage
The incidence of pregnancy wastage by miscarriage or abortion is higher in patients undergoing stimulation of follicular growth for ovulation induction or ART than in the normal population.

Ectopic pregnancy
Women with a history of tubal disease are at risk of ectopic pregnancy, whether the pregnancy is obtained by spontaneous conception or with fertility treatments. The prevalence of ectopic pregnancy after IVF was reported to be 2 to 5%, as compared to 1 to 1.5% in the general population.

Reproductive system neoplasms
There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for infertility treatment. It is not yet established whether or not treatment with gonadotrophins increases the baseline risk of these tumors in infertile women.

Congenital malformation
The prevalence of congenital malformations after ART may be slightly higher than after spontaneous conceptions. This is thought to be due to differences in parental characteristics (e.g. maternal age, sperm characteristics) and multiple pregnancies.

Thromboembolic events
In women with generally recognised risk factors for thrombo-embolic events, such as personal or family history, treatment with gonadotrophins may further increase the risk. In these women, the benefits of gonadotrophin administration need to be weighed against the risks. It should be noted however, that pregnancy itself also carries an increased risk of thrombo-embolic events.

Treatment in men
Elevated endogenous FSH levels are indicative of primary testicular failure. Such patients are unresponsive to GONAL-f/hCG therapy. Semen analysis is recommended 4 to 6 months after the beginning of treatment in assessing the response.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of GONAL-f with other agents used to stimulate ovulation (e.g. hCG, clomiphene citrate) may potentiate the follicular response, whereas concurrent use of a GnRH agonist to induce pituitary desensitisation may increase the dosage of GONAL-f needed to elicit an adequate ovarian response. No other clinically significant drug interaction has been reported during GONAL-f therapy. GONAL-f should not be administered as mixture with other medicinal products in the same injection.

4.6 Pregnancy and lactation

Use during pregnancy
There is no indication for use of GONAL-f during pregnancy. No teratogenic risk has been reported, following controlled ovarian hyperstimulation, in clinical use with gonadotrophins. In case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of recombinant hFSH. However, to date, no particular malformative effect has been reported. No teratogenic effect has been observed in animal studies.

Use during lactation
GONAL-f is not indicated during lactation. During lactation, the secretion of prolactin can entail a poor prognosis to ovarian stimulation.

4.7 Effects on ability to drive and use machines

No studies on the effects on ability to drive and use machines have been performed.

4.8 Undesirable effects

Treatment in women

Very Common (> 1/10)

- Ovarian cysts;
- Mild to severe injection site reaction (pain, redness, bruising, swelling and/or irritation at the site of injection);
- Headache.

Common (1/100 – 1/10)
- Mild to moderate OHSS (see section 4.4);
- Abdominal pain and gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal cramps and bloating.

Uncommon (1/1000 – 1/100)
- Severe OHSS (see section 4.4).

Rare (1/10 000 – 1/1000)
- Ovarian torsion, a complication of OHSS

Very rare (< 1/10 000)
- Thromboembolism, usually associated with severe OHSS;
- Mild systemic allergic reactions (erythema, rash or facial swelling).

Treatment in men

Common (1/100 – 1/10)
Gynecomastia, acne and weight gain.

4.9 Overdose
The effects of an overdose of GONAL-f are unknown, nevertheless one could expect ovarian hyperstimulation syndrome to occur, which is further described in Special Warnings and Special Precautions for Use.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: gonadotrophins, ATC code: G03GA05.
GONAL-f is a preparation of follicle stimulating hormone produced by genetically engineered Chinese Hamster Ovary (CHO) cells.

In women, the most important effect resulting from parenteral administration of FSH is the development of mature Graafian follicles.

In clinical trials, patients with severe FSH and LH deficiency were defined by an endogenous serum LH level <1.2 IU/l as measured in a central laboratory. However, it should be taken into account that there are variations between LH measurements performed in different laboratories.

In men deficient in FSH, GONAL-f administered concomitantly with hCG for at least 4 months induces spermatogenesis.

5.2 Pharmacokinetic properties
Following intravenous administration, GONAL-f is distributed to the extracellular fluid space with an initial half-life of around 2 hours and eliminated from the body with a terminal half-life of about one day. The steady state volume of distribution and total clearance are 10 l and 0.6 l/h, respectively. One-eighth of the GONAL-f dose is excreted in the urine.

Following subcutaneous administration, the absolute bioavailability is about 70%. Following repeated administration, GONAL-f accumulates 3-fold achieving a steady-state within 3-4 days. In women whose endogenous gonadotrophin secretion is suppressed, GONAL-f has nevertheless been shown to effectively stimulate follicular development and steroidogenesis, despite unmeasurable LH levels.

5.3 Preclinical safety data
In an extensive range of toxicological, mutagenicity and animal studies (dogs, rats, monkeys), acute and chronic (up to 13 weeks and 52 weeks), no significant findings were observed.
Impaired fertility has been reported in rats exposed to pharmacological doses of follitropin alfa (≥ 40 IU/kg/day) for extended periods, through reduced fecundity.

Given in high doses (≥5 IU/kg/day) follitropin alfa caused a decrease in the number of viable foetuses without being a teratogen, and dystocia similar to that observed with urinary hMG. However, since GONAL-f is not indicated in pregnancy, these data are of limited clinical relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Powder:
Sucrose
Sodium dihydrogen phosphate monohydrate
Disodium phosphate dihydrate
Methionine
Polysorbate 20
Phosphoric acid, concentrated
Sodium hydroxide

Solvent:
Water for Injections

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in 6.6.

6.3 Shelf life
2 years.

For immediate and single use following first opening and reconstitution.

6.4 Special precautions for storage
Do not store above 25°C.
Store in the original package.

6.5 Nature and contents of container
GONAL-f is presented as a powder and solvent for injection. The powder is presented in 3 ml vials (Type I glass), with stopper (bromobutyl rubber) and aluminium flip-off cap. The solvent for reconstitution is presented in either 2 ml vials (Type I glass) with stopper (teflon-coated rubber) or in 1 ml pre-filled syringes (Type I glass) with a rubber stopper.

The product is supplied in packs of 1, 5 or 10 vials with the corresponding number of solvent pre-filled syringes. Not all pack sizes may be marketed.

6.6 Instructions for use, handling and disposal
For single use only.

GONAL-f must be reconstituted with the solvent before use.

GONAL-f may be co-reconstituted with lutropin alfa and co-administered as a single injection. In this case lutropin alfa should be reconstituted first and then used to reconstitute GONAL-f powder.

The reconstituted solution should not be administered if it contains particles or is not clear.

Any unused product or waste material should be disposed of in accordance with local requirements.

Manufacturer: Serono laboratories, Aubonne, Switzerland
or: Industria Farmaceutica Serono SpA, Italy.
Importer: Serono Israel Ltd., 50 Bazel St., Herzelia Pituach 46646.

The Ministry of health had determined the format of this leaflet and its content had been examined and approved. 7/04

גונאל־אף 75 יחידות (5.5 מיקרוגרם)

הוראות להזרקה תת–עורית עצמית

אם את מזריקה גונאל־אף לעצמך, אנא קראי בקפידה את ההוראות הבאות:

- שטפי את ידייך. חשוב שכפות ידייך והפריטים בהם תשתמשי יהיו נקיים ככל האפשר.
- אספי את כל מה שדרוש. בחרי משטח נקי והניחי עליו הכל:
  בקבוקון אבקה המכיל את התרופה גונאל־אף, מזרק המכיל ממס, מחט אחת לערבוב התרופה, מחט חדה עדינה להזרקה תת־עורית, ו–2 ספוגיות אלכוהול.

<u>הכיני את התמיסה להזרקה:</u>
- הסירי את הפקק המגן מבקבוקון האבקה ומהמזרק המכיל ממס.
- הסירי את המכסה מהמחט לערבוב וחברי אותה אל המזרק. הזריקי לאט את כל הממס לתוך בקבוקון האבקה של גונאל־אף (תמונה מס׳ 1).
  ערבבי בעדינות מבלי להוציא את המזרק. אין לנער.

<u>התכונני להזרקה:</u>
- לאחר שהאבקה התמוססה (זה קורה בדרך כלל מהר), בדקי שהתמיסה צלולה וללא חלקיקים. הפכי את הבקבוקון ושאבי בעדינות את התמיסה בחזרה אל המזרק (תמונה מס׳ 2).
- אם הרופא רשם לך יותר מבקבוקון אחד של גונאל־אף, הזריקי שוב את התמיסה אל תוך בקבוקון אבקה נוסף ושאבי שוב את התמיסה אל תוך המזרק, עד שיהיה לך המספר הנכון של בקבוקונים של אבקה מומסת בנוזל. ניתן להמס עד 3 בקבוקונים של גונאל אף עם 1 מ״ל של ממס.
- הוציאי את המזרק מתוך הבקבוקון והחליפי את המחט למחט הזרקה עדינה.
- סלקי את בועות האוויר. אם את רואה בועות אוויר במזרק, אחזי את המזרק כשהמחט מכוונת כלפי מעלה וטלטלי בעדינות את המזרק עד שהאוויר יתרכז בקצה. דחפי את הבוכנה עד שבועות האוויר ייעלמו (תמונה מס׳ 3).

<u>הזריקי מיד את התמיסה:</u>
- הרופא או האחות הורו לך כבר היכן להזריק (לדוגמה בבטן, ברקמת הירך). נגבי את האזור שבחרת עם ספוגית אלכוהול. צבטי את העור בחוזקה והחדירי את המחט בזווית של 45 עד 90 מעלות בתנועה מהירה. הזריקי מתחת לעור, כפי שלימדו אותך. אל תזריקי ישירות אל תוך וריד. הזריקי את התמיסה על ידי לחיצה עדינה על הבוכנה. קחי את כל הזמן הדרוש כדי להזריק את כל התמיסה. לאחר מכן הוציאי מייד את המחט ונקי את העור בתנועה מעגלית עם ספוגית אלכוהול (תמונה מס׳ 4).

- השמידי את כל הפריטים המשומשים. לאחר שסיימת את ההזרקה, השליכי את כל המחטים, המזרק והבקבוקונים הריקים למיכל מתאים.

מינון עודף
ההשפעות של מנה עודפת של גונאל־אף אינן ידועות. עם זאת, ניתן לצפות לתסמונת גירוי־יתר של השחלות, המתוארת בסעיף ״אמצעי זהירות ואזהרות מיוחדות לשימוש״.

יציבות ואחסון
יש לאחסן בקבוקונים של גונאל־אף ומזרקים המכילים ממס בטמפרטורה מתחת ל–25℃, ואין להשתמש בהם לאחר תאריך התפוגה המופיע על האריזה.

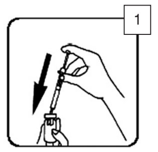
לאחר ההמסה אין לאחסן בטמפרטורה שמעל 25℃. אין להקפיא.
אין להשתמש במקרים, שהתמיסה מכילה חלקיקים ואינה צלולה.
יש לשמור באריזה המקורית כדי להגן מפני אור.

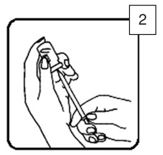
כמויות באריזה
גונאל־אף מופיע באריזות של בקבוקון אחד, 5, או 10 בקבוקונים, לכל בקבוקון מצורף מזרק המכיל 1 מ״ל מי–הזרקה כממס.

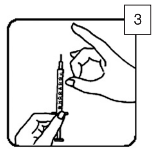
יש לאחסן תרופות הרחק מהישג ידם של ילדים.

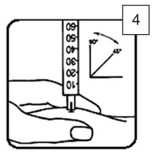
יצרן: סרונו מעבדות, שוויץ.
או: אינדוסטריה פרמצבטיקה, סרונו, איטליה.
יבואן: סרונו ישראל בע״מ, בזל 50, הרצליה פיתוח 46646.

פורמט עלון זה נקבע ע״י משרד הבריאות ותוכנו נבדק ואושר על ידו. 7/04


1


2


3


4