1. NAME OF THE MEDICINAL PRODUCT

GONAL-f™ 1050 IU/1.75 ml (77 micrograms/1.75 ml) powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 77 micrograms of follitropin alfa* equivalent to 1050 IU. Each ml of the reconstituted solution contains 600 IU.
* recombinant human follicle stimulating hormone (r-hFSH) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

For a full list of excipients, see section 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.

The pH of the reconstituted solution is 6.5-7.5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In adult women

- Anovulation (including polycystic ovarian syndrome) in women who have been unresponsive to treatment with clomiphene citrate.

- Stimulation of multifollicular development in women undergoing superovulation for assisted reproductive technologies (ART) such as *in vitro* fertilisation (IVF), gamete intra-fallopian transfer and zygote intra-fallopian transfer.

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 disorders.

Posology
The dose 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 medicinal products. . It is advised to adhere to the recommended starting doses indicated below. Comparative clinical studies have shown that on average patients require a lower cumulative dose and shorter treatment duration with GONAL-f™ compared with urinary FSH. Therefore, it is considered appropriate to give a lower total dose of GONAL-f™ than generally used for urinary FSH, not only in order to optimise follicular development but also to minimise the risk of unwanted ovarian hyperstimulation. See section 5.1.

Bioequivalence has been demonstrated between equivalent doses of the monodose presentation and the multidose presentation of GONAL-f™.

The following table states the volume to be administered to deliver the prescribed dose:

Dose (IU)	Volume to be injected (ml)
75	0.13
150	0.25
225	0.38
300	0.50
375	0.63
450	0.75

The next injection should be done at the same time the next day.

Women with anovulation (including polycystic ovarian syndrome)

GONAL-f™ may be given as a course of daily injections.

In menstruating women treatment should commence within the first 7 days of the menstrual cycle.

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. Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and/or oestrogen secretion. 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 undergo further evaluation after which she may recommence treatment at a higher starting dose than in the abandoned cycle.

When an optimal response is obtained, a single injection of 250 micrograms recombinant human choriogonadotropin alfa (r-hCG) or 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 may be performed.

If an excessive response is obtained, treatment should be stopped and hCG withheld (see section 4.4). Treatment should recommence in the next cycle at a dose 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 of 250 micrograms r-hCG or 5,000 IU 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 gonadotropin-releasing hormone (GnRH) agonist or antagonist 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.

Special population

Elderly population

There is no relevant use of GONAL-f™ in the elderly population. Safety and effectiveness of GONAL-f™ in elderly patients have not been established.

Renal or hepatic impairment

Safety, efficacy and pharmacokinetics of GONAL-f™ in patients with renal or hepatic impairment have not been established.

Paediatric population

There is no relevant use of GONAL-f™ in the paediatric population.

Method of administration

GONAL-f™ is intended for subcutaneous administration. The first injection of GONAL-f™ should be performed under direct medical supervision. Self-administration of GONAL - f™ should only be performed by patients who are well motivated, adequately trained and have access to expert advice.

As GONAL-f multidose is intended for several injections, clear instructions should be provided to the patients to avoid misuse of the multidose presentation.

Due to a local reactivity to benzyl alcohol, the same site of injection should not be used on consecutive days.
Individual reconstituted vials should be for single patient use only.

For instructions on the reconstitution and administration of GONAL-f™ powder and solvent for solution for injection see section 6.6.

4.3 Contraindications

GONAL-f™ must not be used in:

- hypersensitivity to the active substance follitropin alfa, FSH or to any of the excipients
- tumours of the hypothalamus or pituitary gland

In women:

- ovarian enlargement or ovarian 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

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.

Gonadotropin 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 and exaggerated response in others. The lowest effective dose in relation to the treatment objective should be used.

Porphyria

Patients with porphyria or a family history of porphyria should be closely monitored during treatment with GONAL-f™. Deterioration or a first appearance of this condition may require cessation of treatment.

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 appropriate specific treatment given.

Patients undergoing stimulation of follicular growth, whether in the frame of treatment for anovulatory infertility or ART procedures, may experience ovarian enlargement or develop hyperstimulation. Adherence to recommended GONAL-f™ dose and regimen of administration and careful monitoring of therapy will minimise the incidence of such events. For accurate interpretation of the indices of follicle development and maturation, the physician should be 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 gonadotropin (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)

A certain degree of ovarian enlargement is an expected effect of controlled ovarian stimulation. It is more commonly seen in women with polycystic ovarian syndrome and usually regresses without treatment.

In distinction to uncomplicated ovarian enlargement. OHSS is a condition 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 or acute pulmonary distress. Rarely, severe OHSS may be complicated by ovarian torsion or thromboembolic events such as pulmonary embolism, ischaemic stroke or myocardial infarction.

Independent risk factors for developing OHSS include polycystic ovarian syndrome high absolute or rapidly rising serum oestradiol levels (e.g. > 900 pg/ml or > 3,300 pmol/l in anovulation; > 3,000 pg/ml or > 11,000 pmol/l in ART) and large number of developing ovarian follicles (e.g. > 3 follicles of ≥ 14 mm in diameter in anovulation; ≥ 20 follicles of ≥ 12 mm in diameter in ART) and large number of oocytes retrieved in ART cycles.

Adherence to recommended GONAL-f™ dosage and regimen of administration can minimise the risk of ovarian hyperstimulation (see sections 4.2 and 4.8). Monitoring of stimulation cycles by ultrasound scans as well as oestradiol measurements are recommended to early identify risk factors.

There is evidence to suggest that hCG plays a key role in triggering OHSS and that the syndrome may be more severe and more protracted if pregnancy occurs. Therefore, if signs of ovarian hyperstimulation occur such as serum oestradiol level > 5,500 pg/ml or > 20,200 pmol/l and/or ≥ 40 follicles in total, it is recommended that hCG be withheld and the patient be advised to refrain from coitus or to use barrier contraceptive methods for at least 4 days. As OHSS may progress rapidly (within 24 hours) or over several days to become a serious medical event, patients should be followed for at least two weeks after hCG administration.

In ART, aspiration of all follicles prior to ovulation may reduce the occurrence of hyperstimulation.

Mild or moderate OHSS usually resolves spontaneously. If severe OHSS occurs, it is recommended that gonadotropin treatment be stopped if still ongoing and that the patient be hospitalised and appropriate therapy be started.

Multiple pregnancy

In patients undergoing ovulation induction, the incidence of multiple pregnancy is increased compared with natural conception. The majority of multiple conceptions are twins. Multiple pregnancy, specially high order, carries an increase risk in adverse maternal and perinatal outcomes. To minimise the risk of multiple pregnancy, careful monitoring of ovarian response is 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 loss

The incidence of pregnancy loss by miscarriage or abortion is higher in patients undergoing stimulation of follicular growth for ovulation induction or ART than following natural conception.

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 ART was reported to be higher than 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 gonadotropins increases the risk of these tumours 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 recent or ongoing thromboembolic disease or women with generally recognised risk factors for thrombo-embolic events, such as personal or family history, treatment with gonadotropins may further increase the risk for aggravation or occurrence of such events. In these women, the benefits of gonadotropin administration need to be weighed against the risks. It should be noted however, that pregnancy itself as well as OHSS, also carry an increased risk of thrombo-embolic events.

Sodium content

GONAL-f™ contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of GONAL-f™ with other medicinal products used to stimulate ovulation (e.g. hCG, clomiphene citrate) may potentiate the follicular response, whereas concurrent use of a GnRH agonist or antagonist to induce pituitary desensitisation may increase the dosage of GONAL-f™ needed to elicit an adequate ovarian response. No other clinically significant medicinal product interaction has been reported during GONAL-f™ therapy.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is no indication for use of GONAL-f™ during pregnancy. Data on a limited number of exposed pregnancies (less than 300 pregnancy outcomes) indicate no malformative or feto/ neonatal toxicity of follitropin alfa. No teratogenic effect has been observed in animal studies (see section 5.3). In case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of GONAL-f™.

Breastfeeding
GONAL-f™ is not indicated during lactation. During lactation, the secretion of prolactin can result in a poor prognosis to ovarian stimulation.

Fertility

GONAL-f™ is indicated for use in infertility (see section 4.1).

4.7 Effects on ability to drive and use machines

GONAL-f™ is expected to have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The most commonly reported adverse reactions are headache, ovarian cysts and local injection site reactions (e.g. pain, erythema, haematoma, swelling and/or irritation at the site of injection).

Mild or moderate ovarian hyperstimulation syndrome (OHSS) have been commonly reported and should be considered as an intrinsic risk of the stimulation procedure. Severe OHSS is uncommon (see section 4.4).

The following definitions apply to the frequency terminology used hereafter:

Very common (≥ 1/10)
Common (≥ 1/100, < 1/10)
Uncommon (≥ 1/1,000, < 1/100)
Rare (≥ 1/10,000, < 1/1,000)
Very rare (< 1/10,000)

The following adverse reactions may be observed after administration of GONAL-f™.

Treatment in women
Immune system disorders
Very rare: Mild to severe hypersensitivity reactions including anaphylactic reactions and shock

Respiratory, thoracic and mediastinal disorders
Very rare: Exacerbation or aggravation of asthma

General disorders and administration site conditions
Very common: Injection site reactions (e.g. pain, erythema, haematoma, swelling and/or irritation at the site of injection)

Nervous system disorders
Very common: Headache

Vascular disorders
Rare: Thromboembolism

Gastrointestinal disorders
Common: Abdominal pain, abdominal distension, abdominal discomfort, nausea, vomiting, diarrhoea

Reproductive system and breast disorders
Very common: Ovarian cysts
Common: Mild or moderate OHSS (including associated symptomatology)
Uncommon: Severe OHSS (including associated symptomatology) (see section 4.4)
Rare: Complication of severe OHSS

4.9 Overdose

The effects of an overdose of GONAL-f™ are unknown.Nevertheless, there is a possibility that OHSS may occur (see section 4.4)

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital systems, gonadotropins, ATC code: G03GA05.

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

In women with anovulation, 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.

Clinical efficacy and safety in women
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 clinical studies comparing r-hFSH (follitropin alfa) and urinary FSH in ART (see table below) and in ovulation induction, GONAL-f™ was more potent than urinary FSH in terms of a lower total dose and a shorter treatment period needed to trigger follicular maturation.
In ART, GONAL-f™ at a lower total dose and shorter treatment period than urinary FSH, resulted in a higher number of oocytes retrieved when compared to urinary FSH.

Table: Results of study GF 8407 (randomised parallel group study comparing efficacy and safety of GONAL-f™ with urinary FSH in assisted reproduction technologies)

	GONAL-f™ (n = 130)	**urinary FSH (n = 116)**
Number of oocytes retrieved	11.0 ± 5.9	8.8 ± 4.8
Days of FSH stimulation required	11.7 ± 1.9	14.5 ± 3.3
Total dose of FSH required (number of FSH 75 IU ampoules)	27.6 ± 10.2	40.7 ± 13.6
Need to increase the dose (%)	56.2	85.3

Differences between the 2 groups were statistically significant ($p < 0.05$) for all criteria listed.

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 gonadotropin secretion is suppressed, follitropin alfa has nevertheless been

shown to effectively stimulate follicular development and steroidogenesis, despite unmeasurable LH levels.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity and genotoxicity additional to that already stated in other sections of this package insert.

In rabbits, the formulation reconstituted with 0.9 % benzyl alcohol and 0.9 % benzyl alcohol alone, both resulted in a slight haemorrhage and subacute inflammation after single subcutaneous injection or mild inflammatory and degenerative changes after single intramuscular injection respectively.

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 Menopausal Gonadotropin (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
Phosphoric acid, concentrated
Sodium hydroxide

Solvent

Water for injections
Benzyl alcohol

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Please refer to expiry date on outer carton.

The reconstituted solution is stable for 28 days at or below 25°C.

6.4 Special precautions for storage

Prior to reconstitution, do not store above 25°C. Store in the original package, in order to protect from light
After reconstitution, do not store above 25°C. Do not freeze. Store in the original container, in order to protect from light.

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 rubber stopper (bromobutyl rubber) and aluminium flip-off cap. The solvent for reconstitution is presented in 2 ml pre-filled syringes (Type I glass) with a rubber stopper. The administration syringes made of polypropylene with a stainless steel pre-fixed needle are also provided.

The medicinal product is supplied as a pack of 1 vial of powder with 1 pre-filled syringe of solvent for reconstitution and 15 disposable syringes for administration graduated in FSH units.

6.6 Special precautions for disposal and other handling

GONAL-f™ 1050 IU/1.75 ml (77 micrograms/1.75 ml) must be reconstituted with the 2 ml solvent provided before use.
GONAL-f™ 1050 IU/1.75 ml (77 micrograms/1.75 ml) preparation must not be reconstituted with any other GONAL-f™ containers.
The solvent pre-filled syringe provided should be used for reconstitution only and then disposed of in accordance with local requirements. A set of administration syringes graduated in FSH units is supplied in the GONAL-f™ multidose box. Alternatively, a 1 ml syringe, graduated in ml, with pre-fixed needle for subcutaneous administration could be used (see section "How to prepare and use the GONAL-f™ powder and solvent" below).

The reconstituted solution should not be administered if it contains particles or is not clear.Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

HOW TO PREPARE AND USE THE GONAL-f™ POWDER AND SOLVENT

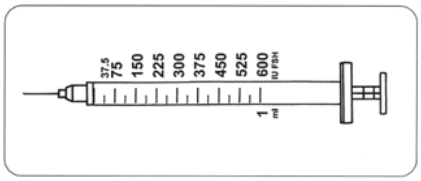
- *This section tells you how to prepare and use your GONAL-f™ powder and solvent.*
- *Before starting the preparation, please read these instructions the whole way through first.*
- *Give yourself the injection at the same time each day.*

1. Wash your hands and find a clean area

- *It is important that your hands and the items you use be as clean as possible.*
- *A good place is a clean table or kitchen surface.*

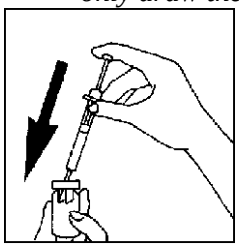
2. Get together everything you need and lay them out:*:*

- *2 alcohol swabs*
- *The pre-filled syringe containing the solvent (the clear liquid)*
- *The vial containing GONAL-f™ (the white powder)*
- *An empty syringe for injection (see illustration below)*



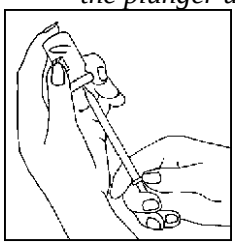
3. Preparing the solution

- *Remove the protective caps from the powder vial and from the pre-filled syringe.*
- *Take your pre-filled syringe, insert the needle into the powder vial and slowly inject all the solvent (2 ml) into the vial containing the powder.*
- *Remove the syringe from the vial and throw it away (put the protective cap to avoid injuries).*
- *This vial contains several doses of GONAL-f™. You will have to keep it several days and only draw the prescribed dose every day.*



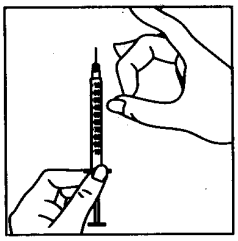
4. Getting ready the syringe for injection

- *Swirl gently the vial of GONAL-f™ prepared in step 3, do not shake. Check that the solution is clear and does not contain any particles.*
- *Take the syringe for injection and fill it with air by pulling the plunger to the correct dose in International Units (IU FSH).*
- *Insert the needle into the vial, turn the vial upside down and inject the air into the vial.*
- *Draw the prescribed dose of GONAL-f™ into the syringe for administration by pulling the plunger until it reaches the correct dose in IU FSH.*



5. Removing air bubbles

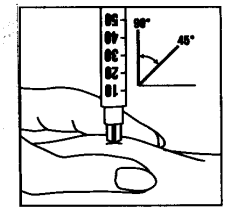
- *If you see air bubbles in the syringe, hold the syringe with the needle pointing upwards and gently flick the syringe until all the air collects at the top. Push the plunger until the air bubbles are gone.*



6. Injecting the dose

- *Immediately inject the solution: Your doctor or nurse will have already advised you where to inject (e.g. tummy, front of thigh). To minimise skin irritation, select a different injection site each day.*
- *Clean the chosen skin area with an alcohol swab using a circular motion.*

- *Firmly pinch the skin together and insert the needle at a 45° to 90° angle using a dart-like motion.*
- *Inject under the skin by pushing gently the plunger, as you were taught. Do not inject directly into a vein. Take as much time as you need to inject all the solution.*
- *Immediately withdraw the needle and clean the skin with an alcohol swab using a circular motion.*



7. After the injection

- *Once you have finished your injection, immediately discard the used syringes safely, preferably in a sharp container.*
- *Store the glass vial with the prepared solution in a safe place. You may need it again. The prepared solution is for your use alone and must not be given to other patients.*
- *For further injections with the prepared solution of GONAL-f™, repeat steps 4. to 7.*

Manufacturer
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