Professional information

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

GONAL-f 300 IU/0.5 ml Solution for injection

GONAL-f 450 IU/0.75 ml Solution for injection

GONAL-f 900 IU/1.5 ml Solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

GONAL-f 300 IU/0.5 ml. Each ml of solution contains 600 IU of follitropin alfa* (equivalent to 44 micrograms). Each pre-filled multidose pen delivers 300 IU (equivalent to 22 micrograms) in 0.5 ml.

GONAL-f 450 IU/0.75 ml. Each ml of solution contains 600 IU of follitropin alfa* (equivalent to 44 micrograms). Each pre-filled multidose pen delivers 450 IU (equivalent to 33 micrograms) in 0.75 ml.

GONAL-f 900 IU/1.5 ml. Each ml of solution contains 600 IU of follitropin alfa* (equivalent to 44 micrograms). Each pre-filled multidose pen delivers 900 IU (equivalent to 66 micrograms) in 1.5 ml.

*Recombinant human follicle stimulating hormone (r-hFSH) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

Sugar-free

For a full list of excipients, see Section 6.1.

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

3. PHARMACEUTICAL FORM

GONAL-f 300 IU/0.5 ml; GONAL-f 450 IU/0.75 ml; GONAL-f 900 IU/1.5 ml:

Solution for injection in pre-filled pen.

Clear colourless solution.

The pH of the solution is 6.7 – 7.3

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 multi-follicular development in patients undergoing superovulation for assisted reproductive technologies (ART) such as *in vitro* fertilisation (IVF), gamete intra-fallopian transfer (GIFT) and zygote intra-fallopian transfer (ZIFT).
- GONAL-f in association with a luteinising hormone (LH) preparation is recommended for the stimulation of follicular development in women with severe LH and FSH deficiency.

In adult men:

- GONAL-f is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism with concomitant human Chorionic Gonadotropin (hCG) therapy.

4.2 Posology and method of administration

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

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 dosage and shorter treatment duration with GONAL-f compared with urinary FSH. Therefore, it is considered appropriate to give a lower total dosage 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.

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

The injection site should be alternated daily.

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 IU – 75 IU at 7- or 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 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 (r-hCG) administration. Alternatively, intrauterine insemination (IUI) may be performed.

If an excessive response is obtained, treatment should be stopped and r-hCG withheld (see section 4.4). 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 fertilization or other assisted reproductive technologies*:**

A commonly used regimen for superovulation involves the administration of 150 -225 IU of GONAL-f, 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 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 250 micrograms r-hCG or 5,000 IU up to 10 000 IU human Chorionic Gonadotropin (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 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.

Women with anovulation resulting from severe LH and FSH deficiency:

In LH and FSH deficient women (hypogonadotrophic hypogonadism), the objective of GONAL-f therapy in association with lutropin alfa is to develop a single mature Graafian follicle from which the oocyte will be liberated after the administration of human Chorionic Gonadotropin (hCG). GONAL-f should be given as a course of daily injections simultaneously with lutropin alfa. Since these patients are amenorrhoeic and have low endogenous oestrogen secretion, treatment can commence at any time.

A recommended regimen commences at 75 IU of lutropin alfa daily with 75-150 IU FSH. Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and oestrogen response.

If an FSH dose increase is deemed appropriate, dose adaptation should preferably be after 7- to 14-day intervals and preferably by 37.5 IU – 75 IU increments. It may be acceptable to extend the duration of stimulation in any one cycle up to 5 weeks.

When an optimal response is obtained, a single injection of 250 micrograms r-hCG or 5,000 IU up to 10,000 IU hCG should be administered 24 to 48 hours after the last GONAL-f and lutropin alfa injections. The patient is recommended to have coitus on the day of, and on the day following, hCG administration. Alternatively, intrauterine insemination (IUI) may be performed.

Luteal phase support may be considered since lack of hormones with luteotrophic activity (LH/hCG) after ovulation may lead to premature failure of the *corpus luteum.*

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

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.

Special populations

Elderly

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 use. The injection should be given at the same time each day.

The first injection 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 pre-filled pen with multidose cartridge is intended for several injections, clear instructions should be provided to the patients to avoid misuse of the multidose presentation.

For instructions on the administration with the pre-filled pen, see section 6.6 and the “Instructions for use”.

4.3 Contraindications

GONAL-f must not be used in patients with:

- hypersensitivity to follitropin alfa, or to any of the excipients listed in section 6.1
- tumours of the hypothalamus or pituitary gland
- ovarian enlargement or ovarian cyst of unknown aetiology
- 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:

- primary ovarian failure
- malformations of sexual organs incompatible with pregnancy
- fibroid tumours of the uterus incompatible with pregnancy.
- primary testicular insufficiency

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

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

Gonadotropin therapy requires an appropriate commitment by medical practitioners 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 inter-patient 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 in both men and women.

Porphyria

Patients with porphyria or a family history of porphyria should be closely monitored during treatment with GONAL-f. Exacerbation 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 as 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 medical practitioner(s) 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- to 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 that 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).

Adherence to recommended GONAL-f dose 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. OHSS may progress rapidly (within 24 hours) or over several days to become a serious medical event. It most often occurs after hormonal treatment has been discontinued and reaches its maximum at about seven to ten days following treatment. Therefore, patients should be followed up 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 induction of ovulation, the incidence of multiple conception is increased compared with natural conception. The majority of multiple conceptions are twins.
Multiple conceptions, especially of high order, carries an increased risk in adverse maternal and perinatal outcomes.

To minimise the risk of higher order multiple conceptions, careful monitoring of ovarian response is recommended.

In patients undergoing ART procedures the risk of multiple conceptions 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 treatment 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 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.

Treatment in men

Elevated endogenous FSH levels are indicative of primary testicular failure. Such patients are unresponsive to GONAL-f/hCG therapy. GONAL-f should not be used when an effective response cannot be obtained.

Semen analysis is recommended 4 to 6 months after the beginning of treatment as part of the assessment of the response.

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 dose of GONAL-f needed to elicit an adequate ovarian response. No other clinically significant drug 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 foeto/neonatal toxicity of follitropin alfa.

No teratogenic effect has been observed in animal studies (see section 4.1). In case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of GONAL-f

Lactation

GONAL-f is not indicated during lactation.

Fertility

GONAL-f is indicated for use in infertility.

4.7 Effects on ability to drive and use machinery

It is not expected that this medicine will affect the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile:

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

Thromboembolism may occur very rarely (see section 4.4).

List of adverse reactions:

Adverse reactions reported are listed below by system organ class and by frequency.

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)

Treatment in women

Immune system disorders

Very rare: Mild to severe hypersensitivity reactions including anaphylactic reactions and shock

Nervous system disorders

Very common: Headache

Vascular disorders

Very Rare: Thromboembolism (both in association with and separate from OHSS)

Respiratory, thoracic and mediastinal disorders

Very rare: Exacerbation or aggravation of asthma

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)

Rare: Complication of severe OHSS

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)

Treatment in Men

Immune system

Very rare: Mild to severe hypersensitivity reactions including anaphylactic reactions and shock

Respiratory, thoracic and mediastinal disorders

Very rare: Exacerbation or aggravation of asthma

Skin and subcutaneous tissue disorders

Common: Acne

Reproductive system and breast disorders

Common: Gynaecomastia, varicocele

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).

Investigations

Common: Weight gain

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04. Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

The effects of an overdose of GONAL-f are unknown, nevertheless, there is a possibility that OHSS may occur.

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.

Clinical efficacy and safety in men

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, follitropin alfa 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 follitropin alfa dose is excreted in the urine.

Following subcutaneous administration, the absolute bioavailability is about 70 %. Following repeated administration, follitropin alfa 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 leaflet.

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 fetuses 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

Inactive ingredients: Poloxamer 188, Sucrose, Methionine, Sodium dihydrogen phosphate monohydrate, Disodium phosphate dihydrate, m-Cresol, Phosphoric acid, concentrated, Sodium hydroxide, Water for injections

6.2 Incompatibilities

None

6.3 Shelf life

24 months.

Once opened, the medicinal product may be stored for a maximum of 28 days at or below 25 ºC.

The patient should write on the GONAL-f pre-filled pen the day of the first use.

6.4 Special precautions for storage

Store at 2 – 8 °C (in a refrigerator). Do not freeze.

Before opening and within its shelf life, the medicinal product may be removed from the refrigerator, without being refrigerated again, for a maximum of 28 days at or below 25 ºC. The product must be discarded if it has not been used after 3 months.

Store in the original package in order to protect the product from light.

Keep out of reach of children.

6.5 Nature and contents of container

GONAL-f Pen 300 IU/0,5 mL (22 micrograms/0,5 mL) is supplied as 0,5 mL of a solution for injection in a 3 mL transparent cartridge (Type 1 glass), with a grey plunger stopper (halobutyl rubber) and an aluminium-rubber crimp cap.
The cartridge is preassembled with the pre-filled pen and supplied as a pack of 1 pre-filled pen and 8 needles to be used with the pen for administration.

GONAL-f Pen 450 IU/0,75 mL (33 micrograms/0,75 mL) is supplied as 0,75 mL of a solution for injection in a 3 mL transparent cartridge (Type 1 glass), with a grey plunger stopper (halobutyl rubber) and an aluminium-rubber crimp cap.
The cartridge is preassembled with the pre-filled pen and supplied as a pack of 1 pre-filled pen and 12 needles to be used with the pen for administration.

GONAL-f Pen 900 IU/1,5 mL (66 micrograms/1,5 mL) is supplied as 1,5 mL of a solution for injection in a 3 mL transparent cartridge (Type 1 glass), with a grey plunger stopper (halobutyl rubber) and an aluminium-rubber crimp cap.
The cartridge is preassembled with the pre-filled pen and supplied as a pack of 1 pre-filled pen and 20 needles to be used with the pen for administration.

6.6 Special precautions for disposal and other precautions

See the “Instructions for use”.
The solution should not be administered if it contains particles or is not clear.
Any unused solution must be discarded not later than 28 days after first opening.
GONAL-f solution for injection in pre-filled pens is not designed to allow the cartridge to be removed.
Discard used needles immediately after injection.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE FOR REGISTRATION

Merck (Pty) Ltd

1 Friesland Drive

Longmeadow Business Estate South

Modderfontein, 1645

South Africa

NAME AND ADDRESS OF MANUFACTURER

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8. REGISTRATION NUMBERS

GONAL-f Pen 300 IU/0,5 mL (22 micrograms/0,5 mL)	A39/21.10/0631
GONAL-f Pen 450 IU/0,75 mL (33 micrograms/0,75 mL)	A39/21.10/0632
GONAL-f Pen 900 IU/1,5 mL (66 micrograms/1,5 mL)	A39/21.10/0633

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 March 2002

10. DATE OF REVISION OF THE TEXT

02 December 2021