

## NEW ZEALAND DATA SHEET

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### Name of Medicine

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GONAL-f follitropin alfa (rch) 37.5 IU (2.73 microgram) and 150 IU (10.92 microgram) powder for injection with diluent vial.

GONAL-f follitropin alfa (rch) 75 IU (5.76 microgram) powder for injection with diluent vial or syringe.

GONAL-f follitropin alfa (rch) multidose 600 IU/mL [retrievable doses 1050 IU (76.44 microgram) and 450 IU (32.76 microgram)] powder for injection vial with diluent pre-filled syringe.

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### Presentation

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GONAL-f contains recombinant human follicle stimulating hormone (follitropin alfa, (rch)). CAS registry number 146479-72-3.

Follitropin alfa (rch) is produced by a Chinese Hamster Ovary cell line transfected with the human FSH subunit genes (i.e. by recombinant DNA technology).

GONAL-f is available as a sterile, lyophilised powder containing follitropin alfa 37.5 IU (2.73 microgram), 75 IU (5.46 microgram) and 150 IU (10.92 microgram) (monodose presentations) and Multidose presentations 600 IU/mL [retrievable doses 1050 IU (76.44 microgram) and 450 IU (32.76 microgram)] vials.

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### Uses

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#### **Actions**

In females, the most important effect resulting from parenteral administration of FSH is the development of mature Graafian follicles. To complete follicular maturation and to stimulate ovulation in the absence of an endogenous luteinising hormone (LH) surge, human chorionic gonadotrophin (hCG) is given once monitoring of the patient indicates that sufficient follicular development has occurred. There may be a degree of interpatient variability in response to FSH administration, with lack of response to FSH in some patients. In males, FSH stimulates spermatogenesis without significant effect on the androgen secreting interstitial cells.

#### **Pharmacokinetics**

Following intravenous administration, GONAL-f is distributed to the extracellular fluid space with an initial half-life around 2 hours and eliminated from the body with a terminal half-life of about 1 day. The steady state volume of distribution and total clearance are 10 L (0.17 L/kg) and 0.6 L/h (0.01 L/h/kg), respectively. One-eighth of the GONAL-f dose is excreted in the urine.

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Following subcutaneous administration, the absolute bioavailability is about 70%. Following repeated administration, GONAL-f accumulates 3-fold at 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.

A Phase 1 (study 21903), double blind, crossover study to assess the comparative bioavailability and the safety of a reference GONAL-f and a new formulation of r-hFSH, administered subcutaneously in male and premenopausal female volunteers was conducted. The pharmacokinetic parameters from this study can be seen in Table 1 below.

Parameter	300IU GONAL-f		20ug New r-hFSH	
	N	Value	N	Value
$C_{max}$ (IU/L)	23	7.4 $\pm$ 1.9	22	8.3 $\pm$ 1.9
$T_{max}$ (h)*	23	12.00(8.00-24.05)*	22	12.00(8.00-24.00)*
AUC <sub>last</sub> (IU.h/L)	23	500 $\pm$ 98	22	541 $\pm$ 105
AUC <sub>inf</sub> (IU.h/L)	14	538 $\pm$ 100	13	586 $\pm$ 102
$t_{1/2}$ (h)	14	37 $\pm$ 7	13	39 $\pm$ 7

\* = Median (range)

The pharmacokinetic parameters  $C_{max}$  and AUC<sub>last</sub> did show statistically significant treatment effect. The ratio of means (test/reference) and calculated 90% confidence intervals for  $C_{max}$  and AUC<sub>last</sub> are summarised in Table 2 below.

Parameter	Treatment Ratio			p value
	Lower	Point Estimate	Upper	
$C_{max}$	1.086	1.125	1.166	0.0001
AUC <sub>last</sub>	1.011	1.079	1.151	0.0195

The reason for the statistically significant gender by period interaction is possibly due to the different means of down regulation used for male and female subjects.

### **Indications**

1. The treatment of anovulatory infertility in women who have been unresponsive to clomiphene citrate or where clomiphene citrate is contraindicated.
2. For controlled ovarian hyperstimulation in women undergoing assisted reproductive technologies.
3. GONAL-f is indicated with concomitant human chorionic gonadotrophin (hCG) therapy for the stimulation of spermatogenesis in gonadotrophin-deficient men in whom hCG alone is ineffective.

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### **Dosage and Administration**

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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 administration. The injection site should be alternated daily to prevent lipoatrophy. Self-administration of GONAL-f should 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).

#### **Monodose Reconstitution**

GONAL-f 37.5 IU (2.73 microgram), 75 IU (5.46 microgram) and 150 IU (10.92 microgram) vials should be reconstituted with the solvent provided (Water for Injections) using a gentle swirling motion, shaking should be avoided. The dose should be injected immediately after reconstitution. The reconstituted solution does not contain an antimicrobial preservative and should be used once only and any residue discarded. Each individual reconstituted vial of GONAL-f is for use in a **single patient**.

**Note:** *In order to avoid the injection of large volumes, two or more vials of GONAL-f lyophilised powder (in any combination of the strengths 37.5 IU (2.73 microgram), 75 IU (5.46 microgram) and/or 150 IU (10.92 microgram) may be dissolved in 1 mL of the solvent supplied (Water for Injections).*

#### **Multidose Reconstitution**

GONAL-f Multidose presentations [600 IU/mL (retrievable doses 1050 IU (76.44 microgram) and 450 IU (32.76 microgram))] vials should be reconstituted with all the bacteriostatic solvent provided in a pre-filled syringe (0.9% benzyl alcohol in Water for Injections) using a gentle swirling motion, shaking should be avoided. The table below states the volume to be administered to deliver the prescribed dose:

Each mL of reconstituted solution contains 600 IU of GONAL-f. The reconstituted solution must not be administered if it contains particles or is not clear.

**Individual reconstituted vials should be for single patient use only. And after the first dose the multidose product should be kept by the patient.**

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

**Note:** *The Reconstituted solution must be stored at 2° to 8°C (Refrigerate. Do not Freeze) and used within 14 days.*

#### **Women with anovulatory infertility (WHO Group II)**

The objective 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 (i) follicle size by ultrasound and/or (ii) oestrogen secretion. A commonly used regimen commences at 75-150 IU (5.46 to 10.92 microgram) FSH daily and is increased by 37.5

IU (2.73 microgram) up to 75 IU (5.46 microgram) at 7 or 14 day intervals if necessary, to obtain an adequate, but not excessive response. If a patient fails to respond adequately after 5 weeks of treatment, that cycle should be abandoned.

When an optimal response is obtained, single injection of 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.

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

### **Women undergoing assisted reproductive technologies**

A commonly used regimen for superovulation involves the administration of 150 IU (10.92 microgram) to 225 IU (16.5 microgram) 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 (32.76 microgram) daily.

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. In clinical trials, final follicular maturation was judged to be when at least two follicles were  $\geq$  16mm mean diameter and when E<sub>2</sub> levels were within the physician's acceptable range for the number of follicles present.

Down-regulation with either 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. Dosage regimes should be customised in order to achieve the desired result. 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 treatment with an agonist, 225 IU (16.5 microgram) GONAL-f is administered (subcutaneously) for the first 7 days. The dose is then adjusted according to the ovarian response.

### **Men with hypogonadotropic hypogonadism**

Prior to combined therapy with GONAL-f and hCG, pre-treatment should begin with hCG alone at the appropriate dosage to achieve masculinisation and serum testosterone level within the eugonadal range ( $\geq$  9-10nM/L). This starting dose should be increased to the necessary dosage in order to obtain normal testosterone values. If after an inadequate trial of hCG alone (usually 6 months) at effective doses, GONAL-f should be given concomitantly at the dosage of 150 IU (10.92 microgram) three times a week. This regimen should be continued for a minimum of 4 months. If after this period, the patient has not responded, the combination treatment (hCG plus GONAL-f 150 IU (10.92 microgram) 3 times a week) may be continued. Current clinical experience indicates that prolonged treatment for up to 18-24 months may be necessary to achieve spermatogenesis or fertility.

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## **Contraindications**

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GONAL-f is contraindicated for safety reasons in:

- cases of prior hypersensitivity to -folliotropin alfa, or to any excipients of GONAL-f

- tumours of the hypothalamus or pituitary gland

FSH therapy is contraindicated for safety reasons where the following exist:

**In women**

- pregnancy and lactation
- ovarian enlargement or ovarian cyst of unknown aetiology
- organic causes of vaginal bleeding
- abnormal uterine bleeding
- sex hormone dependent tumours of the reproductive organs and breast.

FSH is contraindicated when an effective response cannot be obtained, such as:

**In women**

- primary ovarian failure as indicated by high levels of FSH (ovarian dysgenesis, premature menopause)
- organic disorders of the reproductive organs incompatible with pregnancy such as congenital malformations of the uterus and fibroids.

**In men**

- Elevated gonadotrophin levels indicate primary testicular failure
- Infertility disorders other than hypogonadotrophic hypogonadism.

***Use in Elderly and Children***

GONAL-f should not be used in the elderly or children.

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**Warnings and Precautions**

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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 physician 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 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.

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, hyperprolactinaemia, and appropriate specific treatment given.

GONAL-f should be used with caution in patients with known hypersensitivity to gonadotrophin presentations that do not contain FSH, due to the risk of cross-sensitivity. The first injection of GONAL-f in such patients must be performed under direct medical

supervision.

### **Treatment in women**

Patients should be selected carefully according to the following guidelines: a thorough gynaecological and endocrinological evaluation must be performed; presence of early pregnancy should be ruled out; aetiology of any abnormal vaginal bleeding should be established before starting GONAL-f therapy; evaluation of semen quality of the partner should be performed; or other appropriate investigations should be performed as required.

### **Ovarian Hyperstimulation Syndrome (OHSS)**

Mild to moderate uncomplicated ovarian enlargement which may be accompanied by abdominal distension and/or abdominal pain occurs in approximately 20% of those treated with follitropin and hCG, and generally regresses without treatment within two or three weeks. In the presence of ovarian enlargement, treatment should be discontinued.

Patients undergoing superovulation are at an increased risk of developing Ovarian Hyperstimulation Syndrome (OHSS) in view of the excessive oestrogen response and multiple follicular development. Distinct from 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.

OHSS can become a serious complication of human gonadotrophin therapy and sometimes leads to fatal complications if not adequately treated.

Mild manifestations of OHSS include abdominal pain, abdominal discomfort and distension, and enlarged ovaries. Moderate OHSS may additionally present with nausea, vomiting, ultrasound evidence of ascites and marked ovarian enlargement. Severe OHSS further includes symptoms such as severe ovarian enlargement, weight gain, dyspnoea or oliguria.

Clinical evaluation may reveal hypovolaemia, haemoconcentration, electrolyte imbalances, ascites, pleural effusions or acute pulmonary distress. Very 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 have been reported to include young age, lean body mass, polycystic ovarian syndrome, higher doses of exogenous gonadotrophins, high absolute or rapidly rising serum oestradiol levels and previous episodes of OHSS, large number of developing ovarian follicles and large number of oocytes retrieved in ART cycles.

Careful monitoring of ovarian response with ultrasound alone or preferably in combination with measurement of oestradiol levels is recommended prior to and during stimulation therapy, especially in patients with Polycystic Ovarian Syndrome (PCOS).

OHSS may progress rapidly (within 24 hours) or over several days to become a serious medical event. It most often occurs after treatment with follitropin or hCG has been

discontinued, reaching its maximum at about seven to ten days following treatment. Therefore, patients should be followed for at least two weeks after follitropin or hCG administration.

If there are any symptoms or signs of OHSS, the patient must be evaluated, investigated, and monitored. Adherence to recommended GONAL-f dosage and regimen of administration can minimise the risk of OHSS. Monitoring of stimulation cycles by ultrasound scans as well as oestradiol measurements are recommended to identify risk factors early

Excessive oestrogenic response seldom gives rise to significant hyperstimulation unless hCG is administered to induce ovulation. Cases of OHSS are more common, more severe and more protracted if pregnancy occurs. Therefore, if signs of OHSS occur, it is recommended that hCG be withheld and the physician should advise the patient to refrain from intercourse for at least 4 days. Intercourse should be prohibited in those patients in whom significant ovarian enlargement occurs after ovulation because of the danger of haemoperitoneum resulting from ruptured ovarian cysts.

Mild or moderate OHSS requires careful monitoring and may resolve spontaneously. Worsening of symptoms suggests progression of OHSS and requires prompt clinical reassessment. If necessary, the physician should recommend cessation of treatment or withholding hCG injection, and closely monitor the ovarian response. Severe OHSS requires admission to hospital and commencement of appropriate therapy in addition to cessation of gonadotrophins treatment. Treatment of OHSS is primarily symptomatic, consisting of bed rest, fluid and electrolyte management, and analgesics if needed.

The phenomenon of haemoconcentration associated with fluid loss into the peritoneal cavity, pleural cavity and pericardial cavity has been seen to occur and should be thoroughly assessed in the following manner 1) fluid intake and output, 2) weight, 3) haematocrit, 4) serum and urinary electrolytes, 5) urine specific gravity 6) BUN and creatinine and 7) abdominal girth. These determinations are to be performed daily or more often if the need arises. Appropriate imaging examination, especially ultrasound, should also be used for identifying, localising and quantifying fluid loss.

There is an increased risk of injury to the ovary with OHSS. The ascitic, pleural and pericardial fluids should not be removed unless absolutely necessary to relieve symptoms such as pulmonary distress or cardiac tamponade. Pelvic examination may cause rupture of an ovarian cyst, which may result in haemoperitoneum and should therefore be avoided. If this does occur, and if bleeding becomes such that surgery is required, the surgical treatment should be designed to control bleeding and to retain as much ovarian tissue as possible.

### **Thromboembolic Events**

Thromboembolic events, included thrombophlebitis, pulmonary embolism, stroke and arterial occlusion both in association with, and separate from Ovarian Hyperstimulation Syndrome have been reported following gonadotrophin therapy. In rare cases, thromboembolic events have resulted in death.

In women with recent or ongoing thromboembolic disease or women with generally recognised risk factors for thromboembolic events, such as personal or family history, treatment with gonadotrophins may further increase the risk for aggravation or occurrence of such events. In these women, the benefits of gonadotrophin

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 thromboembolic events.

### **Multiple Pregnancies**

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

In patients undergoing induction of ovulation, the incidence of multiple pregnancy is increased compared with natural conception. The majority of multiple conceptions are twins. Multiple pregnancies, especially higher order, carry an increased risk of adverse maternal and perinatal outcomes.

The incidence of multiple pregnancy can be minimised by using the recommended dose and schedule of administration (see 'Dosage and Administration'). Careful monitoring of ovarian response is recommended.

### **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, but comparable with the rates found in women with other fertility problems.

### **Use in Pregnancy (Category D)**

Follitropin alfa is not intended for use during pregnancy (see 'Contraindications'). In rats and rabbits, follitropin alfa caused dystocia and marked postimplantation loss at subcutaneous doses of greater than 5 IU/kg/day, indicating that it is embryotoxic and fetotoxic. Follitropin alfa was not teratogenic at subcutaneous doses up to 320 IU/kg/day in rats or 5 IU/kg/day in rabbits.

### **Use in Lactation**

It is not known whether follitropin alfa is excreted in human milk. In lactating rats, follitropin alfa at doses up to 40 IU/kg did not influence lactation or have any effects on the postnatal growth and development of the offspring. Follitropin alfa was measured in the milk in early lactation.

Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in the nursing infant from GONAL-f, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of the drug to the mother.

### **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 in assessing the response to treatment.

### **Paediatric Use**

GONAL-f should not be used in the paediatric population (see 'Contraindications').

### **Use in the Elderly**

GONAL-f should not be used in the elderly population (see 'Contraindications').

### **Porphyria**

In patients with porphyria or a family history of porphyria, GONAL-f may increase the risk

of an acute attack. Deterioration or a first appearance of this condition may require cessation of treatment.

### ***Effects on the Ability to Drive and Use Machines***

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

### ***Carcinogenicity***

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of follitropin alfa.

### ***Genotoxicity***

Follitropin alfa showed no genotoxic activity in a series of assays performed to evaluate its potential to cause gene mutations (Salmonella typhimurium, E. coli and Chinese hamster lung cells) and chromosomal damage (human lymphocytes and mouse micronucleus test).

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## **Adverse Effects**

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The reactions reported below are classified according to frequency of occurrence as follows:

Very Common	$\geq 1/10$
Common	$\geq 1/100$ to $< 1/10$
Uncommon	$\geq 1/1,000$ to $< 1/100$
Rare	$\geq 1/10,000$ to $< 1/1,000$
Very Rare	$\leq 1/10,000$

### ***Treatment in general***

#### **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

### ***Treatment in women***

The following adverse events have been reported during gonadotrophin

#### **Reproductive system and breast disorders**

Very common: Ovarian cyst, mild to moderate ovarian enlargement

Common: Mild to moderate OHSS, intermenstrual bleeding

Uncommon: Severe OHSS

Rare: Complications of severe OHSS, ectopic pregnancy, adnexal torsion associated with ovarian enlargement

**Gastrointestinal disorders**

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

**Nervous system disorders**

Very common: Headache, dizziness

**Vascular disorders**

Very rare: Thromboembolism usually associated with severe OHSS

Refer to 'Warnings and Precautions' for information on symptoms and management of OHSS.

***Treatment in men*****Reproductive system and breast disorders**

Common: Gynaecomastia

**Skin and subcutaneous tissue disorders**

Common: Acne

**Investigations**

Common: Weight gain

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**Interactions**

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***Interactions with other medicines***

No clinically significant drug interactions have been reported during GONAL-f therapy. Concomitant use of GONAL-f with other agents used to stimulate ovulation may potentiate the follicular response, whereas concurrent use of GnRH agonist or antagonist to induce pituitary desensitisation may increase the dosage of GONAL-f needed to elicit an adequate ovarian response.

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**Overdosage**

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The effects of an overdose of GONAL-f are unknown, nevertheless, there is the possibility that Ovarian Hyperstimulation Syndrome (OHSS) may occur (see 'Warnings and Precautions').

Please advise your patients to immediately contact their doctor or the Poisons Information Centre (in Australia telephone 131 126, in New Zealand telephone 0800 764 766) if they are concerned that they have given themselves too much GONAL-f.

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**Pharmaceutical Precautions**

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***Shelf-life:***

24 months

**Monodose Presentations**

Reconstituted GONAL-f must be used immediately. Contains no antimicrobial agent. Use once and discard any residue. Use in one patient on one occasion only. Although not recommended, the solution may be stored at or below 25°C for up to 24 hours.

**Storage:**

The lyophilised product must be stored below 25°C. Protect from light.

**Multidose Presentations**

The Reconstituted solution must be stored at 2°C to 8°C (Refrigerate. Do not Freeze) and used within 14 days.

**Storage:**

The lyophilised product must be stored below 25 °C. Protect from light.

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**Medicine Schedule**

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Prescription Medicine

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**Package Quantities**

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GONAL-f 37.5 IU (2.73 microgram), 75 IU (5.46 microgram) and 150 IU (10.92 microgram) are supplied in packs of 1, or 5 or 10 or 50 vials containing enough FSH to deliver a minimum of 37.5 IU, 75 IU or 150 IU recombinant human FSH in a lyophilised form.

For GONAL-f 37.5 IU (2.73 microgram) and 150 IU (10.92 microgram), each pack also contains a corresponding number of vials containing 1 mL Water for Injections.

For GONAL-f 75 IU (5.46 microgram), each pack also contains a corresponding number of vials or pre-filled syringes containing 1 mL Water for Injections. The presentations containing vial(s) of FSH and Water for Injections in pre-filled syringe(s) also contain corresponding number of needles for reconstitution and needles for administration.

GONAL-f Multidose for Injection [600 IU/mL retrievable dose 450 IU (32.76 microgram)] is supplied as a kit. Each kit contains

1. 1 vial of recombinant human FSH in a lyophilised form.
2. 1 pre-filled syringe containing 1 mL of bacteriostatic solvent (0.9% benzyl alcohol in Water for Injections)
3. 7 disposable syringes for administration, graduated in FSH units

It is for single patient use only.

GONAL-f Multidose for Injection [600 IU/mL retrievable doses 1050 IU (76.44 microgram) is supplied as a kit. Each kit contains

1. 1 vial of recombinant human FSH in a lyophilised form.
2. 1 pre-filled syringe containing 2 mL of bacteriostatic solvent (0.9% benzyl alcohol in Water for Injections)

3. 15 disposable syringes for administration, graduated in FSH units

It is for single patient use only.

## Further Information

### **Clinical Trials**

#### **WHO Group II anovulatory infertile women**

In a controlled study involving 222 randomised patients, cumulative ovulation rate was not significantly different between GONAL-f and urofollitrophin or urinary derived hFSH groups whether analysed on an intention-to-treat or evaluable patient basis. The ovulation rate in each cycle was also not different between the two medicines.

#### **Superovulation in Assisted Reproduction Techniques (ART)**

Study 21884: The safety and efficacy of GONAL-f (r-hFSH, filled-by-mass) versus urofollitrophin (u-hFSH) and its equivalence as compared to GONAL-f old formulation (filled by bioactivity) all administered sub-cutaneously, were assessed in a multicentre, randomised, single blind, phase III study in infertile women undergoing in vitro fertilization (IVF) and embryo transfer. All patients underwent pituitary desensitisation (down-regulation) with a gonadotrophin-releasing hormone agonist prior to and during stimulation of multiple follicular development with one of the three study treatments. Randomisation occurred when pituitary down-regulation was confirmed by an E<sub>2</sub> level of ≤50pg/mL.

The primary efficacy parameter in this study was the number of fertilised oocytes retrieved per patient. 837 patients entered the study, of whom 713 were randomized. Of these, 711 received at least one dose of FSH: 237 patients received GONAL-f (r-hFSH, filled-by-mass), 237 patients received u-hFSH, and 237 patients received GONAL-f old formulation (filled by bioactivity). The number of oocytes retrieved was similar in all treatment groups. The efficacy of GONAL-f (r-hFSH, filled-by-mass) although not superior, led to statistically higher response rates in the number of fertilised oocytes as compared to u-hFSH. The efficacy results are summarised below in Tables 3 and 4:

Table 3: Number of Oocytes Fertilised: Summary Statistics (mean (sd)) by treatment (Study 21884)

Number of patients	Missing	GONAL-f (filled-by-mass)	<u>u-hFSH</u>	Old GONAL-f (filled by bioactivity)	Overall
653	29	6.7(4.1)	6.0(3.7)	6.1(4.3)	6.3(4.0)

Table 4: Number of Oocytes Fertilised: Statistical Comparisons between the treatment Groups by Age and Type of Insemination.

Age	Insemination	GONAL-f (fbm) vs u-hFSH	Estimated difference	90% CI	GONAL-f (fbm) vs GONAL-f (filled by bioactivity)	Estimated difference	95% CI

< 35	IVF	0.257	0.96	[-0.44, 2.36]	0.471	0.62	[-1.07, 2.30]
	ICSI	0.009	1.45	[0.54, 2.36]	0.004	1.64	[0.54, 2.73]
	All	0.002	1.41	[0.66, 2.16]	0.001	1.52	[0.62, 2.41]
>=35	IVF	0.865	-0.20	[-2.18, 1.77]	0.963	-0.06	[-2.61, 2.49]
	ICSI	0.112	-1.58	[-3.21, 0.06]	0.119	-1.56	[-3.53, 0.41]
	All	0.141	-1.04	[-2.20, 0.12]	0.059	-1.35	[-2.76, 0.05]
All	IVF	0.510	0.43	[-0.65, 1.51]	0.826	0.15	[-1.15, 1.44]
	ICSI	0.098	0.78	[0.00, 1.55]	0.083	0.81	[-0.11, 1.73]
	All	0.052	0.74	[0.11, 1.36]	0.082	0.66	[-0.08, 1.40]

fbm: filled-by-mass

441 of 713 patients experienced 1474 adverse events. 145 patients in the GONAL-f (r-hFSH, filled-by-mass) group, 143 patients in the u-hFSH group and 153 patients in the old GONAL-f (filled by bioactivity) group. Most of the reported events were less in the GONAL-f (r-hFSH, filled-by-mass) group when compared to the old GONAL-f (filled by bioactivity) group. Overall, the pattern of adverse events was similar between treatment groups and was consistent with the profile of events reported in this indication.

### Men with Hypogonadotropic Hypogonadism

Male hypogonadotropic hypogonadism is a rare condition; therefore study sizes are limited. Two phase III (open and non-comparative) studies were conducted to assess the efficacy and safety of GONAL-f in combination with hCG in inducing spermatogenesis in men with Hypogonadotropic Hypogonadism (HH). The primary efficacy endpoint was the achievement of a mature sperm density of  $\geq 1.5 \times 10^6/\text{mL}$ . GONAL-f was administered subcutaneously at a dosage of 150 IU three times a week in combination with hCG ( $\geq 2000$  IU twice weekly) for up to 18 months.

The first study was conducted in university clinical centres in France, Germany and UK. A total of 32 patients with complete, primary isolated HH were recruited into this study. They were azoospermic before entering the study; remained so after the pre-treatment phase and none had prior treatment with FSH or gonadotrophin-releasing hormone (GnRH). In the pre-treatment phase, the patients were treated with hCG alone (2000 IU twice weekly for 3-6 months) to first normalise serum testosterone levels before initiating the treatment with GONAL-f. Of 26 patients who received GONAL-f, 19 patients were found to be eligible for efficacy evaluation.

The primary endpoint of a sperm density of  $\geq 1.5 \times 10^6/\text{mL}$  was achieved in 12/19 (63%) patients. Overall 15/19 (79%) patients achieved some spermatogenesis. The median time to initiate spermatogenesis was 9 months.

The second study was conducted in 2 university clinical centres in Australia. A total of 10 patients with severe HH entered the study, but only 8 patients completed the GONAL-f treatment phase. Similar results to the first study were obtained.

The primary endpoint of a sperm density of  $\geq 1.5 \times 10^6/\text{mL}$  were achieved in 5/8 (63%) patients. Overall 7/8 (88%) patients achieved some spermatogenesis. The median time to initiate spermatogenesis was 6 months. The studies also demonstrated that GONAL-f has a good safety profile and is well tolerated over the treatment period of up to 18 months.

### **List of excipients**

GONAL-f monodose presentation, also contains 30 mg sucrose, 1.11 mg sodium phosphate – dibasic dihydrate, 0.45 mg sodium phosphate – monobasic, 0.1 mg methionine, 0.05 mg polysorbate 20, phosphoric acid and sodium hydroxide to adjust pH, as excipients.

GONAL-f multidose presentation, also contains 30 mg sucrose, 1.11 mg sodium phosphate – dibasic dihydrate, 0.45 mg sodium phosphate – monobasic, phosphoric acid and sodium hydroxide (to adjust pH) per vial as excipients.

### **Chemical structure**

Human follicle stimulating hormone (FSH) is a glycoprotein (MW about 30,000) and is characterised by two amino acid chains known as  $\alpha$  and  $\beta$ . The  $\beta$ -chain confers biological activity. The  $\alpha$ -chain is common to all glycoproteins with specificity residing in the  $\beta$ -chain.

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### **Name and address of sponsor**

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GONAL-f is supplied in New Zealand by:  
Healthcare Logistics  
58 Richard Pearce Drive  
Airport Oaks, Auckland

GONAL-f is supplied in Australia by:  
Merck Serono Australia Pty Ltd  
3-4/25 Frenchs Forest Road East  
Frenchs Forest NSW 2086

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### **Date of Preparation**

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01 July 2011

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