

NEW ZEALAND DATA SHEET

1 PRODUCT NAME

GONAL-f® 300 IU/0.48 mL, 450 IU/0.72 mL, 900 IU/1.44 mL solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

GONAL-f is produced by a Chinese Hamster Ovary cell line transfected with the human FSH subunit genes (i.e. by recombinant DNA technology). Each cartridge contains the active ingredient follitropin alfa (rch) (recombinant human follicle stimulating hormone) 300 IU/0.48 mL, 450 IU/0.72 mL or 900 IU/1.44 mL.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Solution for injection in a cartridge pre-assembled in a pen.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

GONAL-f should be administered subcutaneously. The injection site should be alternated daily to prevent lipoatrophy. Self-administration of GONAL-f should only be performed by patients who are well motivated, adequately trained and who have access to expert advice. Each GONAL-f pen is for individual patient use only.

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 1) follicle size by ultrasound and/or

2) 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, a single injection of 250 microgram r-hCG or 5000 IU up to 10,000 IU urinary human chorionic gonadotropin (u-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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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 250 microgram r-hCG or 5000 IU up to 10,000 IU u-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 ≥ 16 mm mean diameter and when E2 levels were within the physician's acceptable range for the number of follicles present.

Down-regulation with either a GnRH agonist or antagonist is now commonly used in order to suppress the endogenous LH surge and to control tonic levels of LH. Dosage regimens 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 ($> 9 - 10$ nmol/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.

4.3 CONTRAINDICATIONS

GONAL-f is contraindicated for safety reasons in:

- cases of prior hypersensitivity to follitropin 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
- gynaecological haemorrhages of unknown aetiology
- ovarian, uterine or breast carcinoma

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)
- malformations of sexual organs incompatible with pregnancy
- fibroid tumours of the uterus incompatible with pregnancy

In men

- elevated gonadotrophin levels that indicate primary testicular failure
- infertility disorders other than hypogonadotropic hypogonadism

Use in Elderly and Children

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Gonadotrophin therapy requires a certain time commitment by physicians and supportive health professionals, as well as the availability of appropriate monitoring facilities. In women, safe and effective use of GONAL-f calls for monitoring of ovarian response with ultrasound, alone or preferably in combination with measurement of serum oestradiol levels, on a regular basis. There may be a degree of 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.

Self-administration of GONAL-f should only be performed by patients who are well motivated, adequately trained and with access to expert advice. During training of the patient for self-administration, special attention should be given to specific instructions for the use of the pre-filled pen.

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 marked 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. 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 (PCOS), 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 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, including thrombophlebitis, pulmonary embolism, stroke and arterial occlusion both in association with, and separate from OHSS, 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 carries an increased risk of thromboembolic events.

Multiple pregnancies

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

To minimise the risk of twins or higher order multiple pregnancy, careful monitoring of ovarian response is recommended. Appropriate management, such as cycle cancellation, should be considered in line with current clinical practice. The incidence of multiple pregnancy can be minimised by using the recommended dose and schedule of administration (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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. Single embryo transfer in good prognosis cycles substantially reduces the risk of multiple pregnancy with little effect on live birth rates.

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.

Congenital anomalies

The prevalence of congenital anomalies after the use of ART may be slightly higher than after spontaneous conceptions. Possible contributing factors include aspects inherent in the couple's infertility, ovulation induction agents, other medicines used in treatment and the ART procedures. While there is no specific evidence from clinical trials or post-marketing data implicating gonadotrophin use in adverse effects on pregnancy, embryonal or foetal development, parturition or postnatal development, ovulation induction agents cannot be excluded as a contributing factor.

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.

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.

Use in the elderly

GONAL-f should not be used in the elderly population (see Section 4.3 CONTRAINDICATIONS).

Paediatric use

GONAL-f should not be used in the paediatric population (see Section 4.3 CONTRAINDICATIONS).

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 a GnRH agonist or antagonist to induce pituitary desensitisation may increase the dosage of GONAL-f needed to elicit an adequate ovarian response.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

See Section 4.1 THERAPEUTIC INDICATIONS.

Use in pregnancy – Pregnancy Category D

Follitropin alfa is not intended for use during pregnancy (see Section 4.3 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. However, adverse events of these medicines include dizziness which could affect the ability to drive or use machines (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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	$< 1/10,000$

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 (e.g. pain, erythema, haematoma, swelling and/or irritation at the site of injection)

Treatment in women

The following adverse events have been reported during gonadotrophin therapy:

Reproductive system and breast disorders

Very common: Ovarian cyst, mild to moderate ovarian enlargement

Common: Mild or moderate OHSS (including symptomatology), intermenstrual bleeding

Uncommon: Severe OHSS (including symptomatology)

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

Rare: Thromboembolism

Refer to 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

Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals in New Zealand are asked to report any suspected adverse reactions at <https://pophealth.my.site.com/carmreportnz/s/>.

4.9 OVERDOSE

The effects of an overdose of GONAL-f are unknown, nevertheless, there is the possibility that OHSS may occur (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

For risk assessment and advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Chemical structure

Human follicle stimulating hormone (FSH) is a glycoprotein (Molecular Weight is about 30,000 Da) and is characterised by two amino acid chains known as α and β . The β -chain confers biological activity. The α -chain is common to all gonadotrophins with specificity residing in the β -chain.

CAS number

146479-72-3

Mechanism of action

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 inter-patient 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.

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 urofollitropin or urinary-derived hFSH (u-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 u-hFSH and its equivalence as compared to GONAL-f old formulation (filled by bioactivity), all administered subcutaneously, were assessed in a multicentre, randomised, single blind, phase III study in infertile women undergoing *in vitro* fertilisation (IVF) and embryo transfer. All patients underwent pituitary desensitisation (down-regulation) with a gonadotrophin-releasing hormone (GnRH) 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 E₂ level of ≤ 50 pg/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 randomised. 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 1 and 2:

Table 1. Number of Oocytes Fertilised: Summary Statistics (mean (SD)) by Treatment (Study 21884)

Number of patients	Missing	GONAL-f (filled-by-mass)	u-hFSH	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 2. 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 old 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 (HH) 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 HH. The primary efficacy endpoint was the achievement of a mature sperm density of ≥ 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 (≥ 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 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.

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 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.

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 I (study IMP 23572), open, randomised, 2-way crossover study to assess the relative bioavailability and the tolerability of r-hFSH of a reference GONAL-f as a monodose freeze-dried formulation and a new multidose liquid formulation, administered subcutaneously in male and pre-menopausal female volunteers with pituitary gonadotrope cell down regulation was conducted. The pharmacokinetic parameters from this study can be seen in Table 3 below.

Table 3. Summary of the statistics (means, point estimate, confidence interval) on pharmacokinetic parameters of r-hFSH by treatment (liquid/test and lyophilised/reference formulation) – Study IMP 23572

Parameter	Test (N = 41)	Reference (N = 40)	Point estimate Ratio test/reference (N = 39)	90% CI range (0.8 – 1.25)
C _{max} (IU/L) (Min – max)	8.99 (4.70 – 16.7)	9.51 (4.00 – 15.1)	0.9175	(0.8855, 0.9505)
AUC _{last} (IU.h/L) (Min – max)	841 (557 – 2280)	844 (462 – 1170)	0.9512	(0.9222, 0.9810)
t _{max} (h)* (Min – max)	15.0 (6.00 – 48.0)	12.0 (4.00 – 48.0)	NA	NA

(*median values for t_{max})

Following the subcutaneous administration of both formulations, the 90% confidence intervals of the mean ratios for the bioavailability metrics, C_{max} and AUC_{last} lie within the pre-defined limits of 0.8 – 1.25 showing bioequivalence of liquid (test) and freeze dried (reference) formulations. Because the observed variability (<10%) was much lower than expected *a priori*, the study allowed the detection of a small difference between the two formulations in rate (about 8%) and extent (about 5%). Suppression of endogenous FSH production was incomplete, probably more so in period 2 compared to period 1 and this probably explains the significant period effect observed. The significant difference seen on t_{max} is probably a function of the diverse mechanisms by which the drug enters the systemic circulation. In subjects where the diffusion processes from the subcutis to the adjacent small blood vessels dominate, earlier t_{max} is observed, whereas, in subjects where flow of FSH through the lymph to the systemic circulation is dominant, a later t_{max} probably occurs. This latter process may be non-linear generating an apparent zero order input over sustained periods in some subjects. The mixture of these processes in the population leads to very high variability in t_{max} so a larger study would be necessary to truly assess the relative magnitude of this parameter for the two formulations.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Poloxamer, sucrose, methionine, dibasic sodium phosphate dihydrate, monobasic sodium phosphate monohydrate, metacresol (as a preservative at a level of 3.07 mg/mL), phosphoric acid, sodium hydroxide and water for injections.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

24 months

The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate. Do not freeze). Protect from light. Should refrigeration be unavailable, GONAL-f can be stored below 25°C for up to 3 months.

After first piercing GONAL-f pen with a needle, GONAL-f may be stored below 25°C for a maximum of 21 days. Store the pen with the cap on, in order to protect the product from light.

6.5 NATURE AND CONTENTS OF CONTAINER

GONAL-f is supplied in a clear glass 3 mL cartridge (Type 1) with plunger stoppers (halobutyl rubber) and a rubber crimp cap (halobutyl rubber), pre-assembled in a pre-filled pen.

GONAL-f is available in the following strengths and pack sizes:

- 300 IU/0.48 mL (21.84 microgram) extractable volume: 1 cartridge of solution for injection pre-assembled in a disposable delivery pen and 8 needles for administration.
- 450 IU/0.72 mL (32.76 microgram) extractable volume: 1 cartridge of solution for injection pre-assembled in a disposable delivery pen and 12 needles for administration.
- 900 IU/1.44 mL (65.52 microgram) extractable volume: 1 cartridge of solution for injection pre-assembled in a disposable delivery pen and 16 needles for administration

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

7 MEDICINE SCHEDULE

Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

9 June 2005

10 DATE OF REVISION

26 May 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
6.1	Additional information identifying metacresol as preservative
4.9	Addition of risk assessment wording in the management of overdose
6.5	Reduction of the number of needles for GONAL-f 900 IU/1.44 mL presentation