

SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of GONAL-f. This scientific discussion has been updated until 1 July 2004. For information on changes after this date please refer to module 8B.

1. Introduction

The active substance of GONAL-f is a recombinant human follicle-stimulating hormone (r-hFSH, Follitropin alfa as INN) produced by genetically engineered Chinese Hamster Ovary (CHO) cells. GONAL-f is presented as a sterile powder for solution for injection in three single-use strengths (37.5 IU, 75 IU and 150 IU) in glass ampoules or vials together with sterile water for injections as solvent in glass ampoules or vials or prefilled syringes. In addition, two multidose presentations (1050 IU/1.75 ml and 450 IU/0.75 ml) are available as sterile powder for solution for injection in glass vials together with bacteriostatic water for injections as solvent in prefilled syringes. The reconstituted product is intended for subcutaneous injection. Moreover, a ready-to-use formulation designed to facilitate the administration of the product is available, in which GONAL-f is presented as a new pharmaceutical form: solution for injection in a pre-filled pen. GONAL-f contains pure r-hFSH as opposed to other preparations that contain variable amounts of Luteinising Hormone (LH).

FSH is an heterodimeric hormone, in which the alpha-subunit (92 amino acids) is common to other glycoprotein hormones and the beta-subunit (111 amino acids) is specific. It is secreted into the bloodstream by the endocrine cells of the anterior pituitary gland. In female, FSH controls ovarian follicular growth and in men it plays an essential role in inducing spermatogenesis.

The therapeutic uses are *Stimulation of multifollicular development in patients undergoing assisted reproductive treatment (ART); Anovulation in women who have been unresponsive to treatment with clomiphene citrate; Stimulation of follicular development in women with severe LH and FSH deficiency; Male hypogonadotropic hypogonadism.* Due to large inter-individual variations, there is no general dosage which can be recommended. Only general guidelines can be given. In *in vitro* fertilisation (IVF) schedules, it is generally associated with GnRH agonists and followed by hCG administration.

The production of GONAL-f by recombinant DNA technology, has the following characteristics:

- it is a urine-independent production process;
- good batch-to-batch consistency is ensured;
- effective purification takes place;
- absence of LH activity;
- the final product is suitable for subcutaneous injection.

2. Part II: Chemical, pharmaceutical and biological aspects

GONAL-f is a sterile powder for solution for injection in four strengths, 37.5 IU, 75 IU, 150 IU and 600IU/ml (there are two presentations for this latter strength: 1050 IU/1.75 ml and 450 IU/0.75 ml), and is presented in glass ampoules or vials. GONAL-f solution for injection in a pre-filled pen contains 44 micrograms/1 ml (600 IU/1 ml) of follitropin alfa and is available in three pack sizes i.e. 300 IU/0.5 ml (22 micrograms/0.5 ml), 450 IU/0.75 ml (33 micrograms/0.75 ml) and 900 IU/1.5 ml (66 micrograms/1.5 ml).

The active ingredient is a recombinant human FSH, a heterodimeric glycoprotein composed of two linked subunits α and β .

The cell line used for the production of r-hFSH is a CHO cell line co-transfected with the relevant plasmids containing the genes coding for the subunits.

Genetic stability has been assessed by the company with several different methods.

The Marketing Authorisation Holder MAH has established master and working cell banks and an extended population doubling bank.

The downstream purification consists of a complex process divided into six phases for which the process validation has been provided by the MAH. The ability of the process to remove / inactivate viruses has been studied and the results submitted are reassuring.

The MAH committed to retain a specific viral clearance step in their manufacturing process, and to provide a six-month progress report concerning validation of the membrane and implementation of an in-house integrity test.

Ultrafiltration and freeze drying steps are part of the manufacturing process.

Following review of the MAH's initial application (December 1993) and responses to the consolidated list of pharmaceutical questions (December 1994), the company submitted additional clarification to the Rapporteur in April 1995.

The application was considered at the Ad Hoc Working Group on Biotechnology and Pharmacy at their April 1995 meeting which recommended the following:

- a positive opinion be given to this application for Marketing Authorisation,
- the shelf-life of the finished product was set at 12 months with the possibility of extension to a longer period provided that further stability data including physico-chemical analytical results are submitted.

On 23 May 1996, the MAH submitted additional information on stability supporting a shelf-life of 24 months.

On 25 February 1999, the CPMP adopted a positive opinion for the new strength GONAL-f 37.5 IU with a shelf-life of 12 months based on real-time stability data only available for 12 months. This shelf-life could be extended provided that stability data over a longer period are presented.

3. Part III: Toxicopharmacological aspects

The properties of GONAL-f have been compared to a reference substance (urinary menopausal FSH: u-hFSH) throughout the dossier.

Pharmacodynamics

The specific pharmacodynamic action has been studied *in vivo*, in a dose-related fashion in rats and in monkeys. The preparations including r-hFSH and urinary-FSH showed similar activity.

Competition binding assays have been carried out *in vitro*, and the shape of competition curves were parallel using r-hFSH, pituitary and urinary derived hFSH and a comparison of ED50 values suggested the following order of potency: r-hFSH ≥ Metrodin ≥ Metrodin HP > WHO 83/575.

General pharmacodynamic studies in rodents and in dogs showed that there is very little general action on the major body systems (cardiovascular, gastrointestinal, renal, respiratory, central and peripheral nervous systems).

A major issue has been to assess to what extent anti-human FSH antibodies may have interfered with the effects observed in animals and therefore lead to an underestimation of FSH toxicity. In fact poor responsiveness to exogenous human gonadotropins suggestive of neutralising antibodies does not occur in monkeys until after the second course of therapy.

As anticipated the repeated administration of r-hFSH as foreign protein resulted in antibodies forming in all species. Despite this, in non-rodent species the serum levels of FSH and the pharmacological effect seen indicate adequate systemic exposure to active FSH.

Pharmacokinetics

Single and repeated dose studies were conducted in rat and monkey and some information was also derived from the toxicity studies.

Greater variation has been observed in the subcutaneous and intramuscular studies, suggesting variable absorption from these sites. Absorption was good with both routes (70+% bioavailability) but was slower by the subcutaneous route.

A point for discussion was whether the biological half-life of r-hFSH changes as a function of the sialic acid content of the peptide. The effect of oligosaccharide composition of a glycoprotein on *in vivo* clearance rate and *in vivo* efficacy is well-known. With pituitary FSH and r-hFSH, the most sialylated isoforms have the longer half-lives and are the more active forms *in vivo*. Since u-hFSH and r-hFSH have similar pharmacokinetic profiles *in vivo* in both animals and humans, it is very likely that they follow the same metabolic pathway, although no specific studies have been carried out to document the hepatic uptake of r-hFSH by the hepatic asialoglycoprotein receptor

In conclusion the animal pharmacodynamic and pharmacokinetic data are compatible with GONAL-f having the same pharmacological characteristics as the natural human hormone.

Toxicology

The observed toxicity of GONAL-f was almost entirely related to the primary pharmacodynamic action of the active substance, namely the stimulation of spermatogenesis, follicle/cyst development in ovaries and trophic effects on uterine endometrium. Exceptions were mild hepatic toxicity in dogs (at a dose of 100 IU/kg/day) and moderate thymic atrophy in monkeys (at a dose of 300 IU/kg/day).

In the subchronic toxicology studies, levels of antibodies were variable after repeated administration. Whereas all rats treated subcutaneously developed anti-human FSH antibodies, they were not found in any dogs treated intravenously and in only 50% of monkeys treated intramuscularly.

Toxicokinetic and clinical studies however confirmed that animals had been exposed to high levels of r-hFSH despite antibody formation.

There was general similarity of toxicological findings in the shorter and longer-term studies, which represent the pharmacological actions of high doses of FSH, demonstrating evidence of the continuous exposure to r-hFSH despite antibody formation. There was no pathological evidence suggestive of the formation of immune complexes.

Toxicity studies have been conducted on different species. No deaths were seen in any study and the overall data showed that r-hFSH has very low toxicity.

Although clinically contra-indicated during pregnancy, reproductive toxicity studies were undertaken with r-hFSH. No teratogenic effects of r-hFSH were demonstrated. Rats showed increased rates of foetal absorption, abortion and stillbirth at doses of 40 IU/kg/day (4 times the maximal human dose) and above. The resorptions were considered to be due to a severe hormonal imbalance during gestation and this was supported by the similar results observed in an hMG group included in the rabbit study.

The Rapporteur and Co-Rapporteur did not consider it necessary to include statements on the environmental risk assessment.

Indication of GONAL-f in male hypogonadotropic hypogonadism

In order to support long-term treatment in men, two additional toxicity studies of 52-week duration were performed in male rats and male monkeys. The findings in both studies indicated no treatment-related effects on clinical signs (except an effect on testes weight), bodyweight, food consumption, ophthalmologic examinations, haematology, clinical chemistry and urinalysis.

In the rat, histological examination revealed an increase in frequency and/or degree of immature spermatid elements in epididymides in the mid-dose and high-dose groups compared to the control group. This was interpreted as an indication of increased testicular germinal cell turnover. In the monkey, histological examination showed tubular dilatation in all animals in the high-dose group generally associated with increased amount of luminal fluid. No other histological changes were observed which were considered to be treatment-related.

No immunocomplexes related to treatment were found in the kidneys of any animal. Due to species difference, virtually all rats treated with GONAL-f developed anti-human FSH antibodies. Antibodies to human FSH were detected in about half of the treated monkeys within the 6th week and in virtually all animals at the end of dosing. Serum testosterone levels were unaffected by treatment at any dose. Serum levels of FSH were apparently dose-related and there was some evidence for accumulation on repeated dosing. There were no local injection site reactions considered to be related to treatment with

r-hFSH in either rats or monkeys. The pre-clinical studies were satisfactory and left no outstanding pre-clinical safety concerns.

4. Part IV: Clinical aspects

The formulation of r-hFSH used in the presented studies was the one that is proposed for marketing.

Pharmacodynamics and pharmacokinetics

One phase I study compared r-hFSH and natural u-FSH. It was performed in a group of 12 healthy women after pituitary desensitisation with GnRH agonists and shows that a single 150 IU daily GONAL-f dose for 7 days is effective in inducing follicular growth. The inter-individual variation observed was considered by the Rapporteur related to variable ovarian sensitivity, rather than differences in FSH pharmacokinetics.

Other Phase I studies have demonstrated that r-hFSH and u-hFSH by the IM route have similar absolute bioavailability both by immunoassay and by *in vitro* bioassay.

The absolute bioavailabilities of r-hFSH by the IM and SC routes are similar when measured by immunoassay.

Table 1: Apparent terminal phase of u-hFSH half-life following IM/SC administration.

REFERENCES	NO. OF SUBJECTS (SEX)	FSH PREPARATION (IU)	ESTIMATED TERMINAL HALF-LIFE (h)
Flamigni et al.; 1985	3 (Female)	hMG (600) (IM)	35
Diczfalusy et al.; 1988	5 (Female)	hMG (150) (IM)	48
Jockenhovel et al.; 1990	7 (Male)	METRODIN (150) (IM)	25
	5 (Male)	METRODIN (450) (IM)	36
Mizunuma et al.; 1990	16 (Male)	METRODIN (150) (IM)	36 ± 16
Le Cottonnec et al.; 1993	12 (Male)	METRODIN (150) (IM)	36 ± 8
		METRODIN (150) (IM)	39 ± 15
		METRODIN (150) (IM)	45 ± 21
SERONO Study GF5117	12 (Female)	GONAL-f (150) (IM)	37 ± 25
Le Cottonnec et al.; 1994		GONAL-f (150) (SC)	37 ± 28

Based on the pre-clinical studies presented, r-hFSH and u-hFSH appear to be equivalent functionally, pharmacokinetically and pharmacodynamically.

Although the IM and SC routes of administration are regarded as equivalent pharmacologically, the pivotal Phase III study was performed only with SC administered GONAL-f. In view of this the Summary of Product Characteristics was amended to mention only the SC route.

Therapeutic efficacy

Stimulation of multifollicular development in patients undergoing assisted reproductive treatment (ART) (ii)

Three clinical studies had been completed. These included a total of 148 subjects, 85 of whom had been treated with r-hFSH. At the time of submission, safety data was also available from an additional 147 patients treated with r-hFSH in nine ongoing studies.

Study GF 5503 is regarded as the major study allowing evaluation of safety and efficacy of GONAL-f compared with u-hFSH (Metrodin) in patients undergoing IVF-ET. This was a randomised parallel group study in which 61 patients received GONAL-f and 63 Metrodin.

Ovulation stimulation in Assisted Reproductive Technology (ART) was considered as the best means of clinically evaluating r-hFSH as it allows the assessment of the follicular response as well as the subsequent steps of the procedure (including the number of pregnancies and live births). The study was designed to detect a difference of a 2-pre-ovulatory follicles (>10mm) difference between treatment groups (106 patients would provide 80% power at the 5% level of significance.)

The mean number of large follicles (equal or greater than 14 mm in diameter) obtained in the two groups differed by 1.4. This difference was statistically significant in favour of greater efficacy of u-hFSH compared with r-hFSH. However, in the subsequent steps of the IVF-ET procedure the mean differences between the two groups were not statistically significant.

As the number of patients in this study was relatively small, it was considered that insufficient data was available to claim equivalent potency between GONAL-f and Metrodin at this stage. A statement to this effect has been added to the SPC (Section 4.2).

Preliminary results of a further study "GF 5533" of similar design to study "GF 5503" are available and demonstrate no significant difference between r-hFSH and u-hFSH in terms of generation of follicles greater or equal to 14 mm in diameter. The company fulfilled its commitment to provide the final report of study GF 5533 on 31 October 1995.

The MAH provided additional data on the relative potency between GONAL-f and u-hFSH from two clinical studies:

- a double-blind, randomised study involving 278 patients (study GF 8407) to compare efficacy and safety of GONAL-f with that of highly purified urinary FSH (Metrodin HP) for inducing superovulation in women undergoing assisted reproductive techniques (ART);
- a single centre, assessor-blind, randomised, parallel group study involving 44 patients (study GF 9180) to compare the safety and efficacy of GONAL-f with follitropin beta to stimulate multiple follicular development prior to IVF-ET in patients pre-treated with a GnRH agonist.

The trial data presented suggested that GONAL-f does indeed require a lower total dose and a shorter treatment period to achieve pre-ovulatory conditions than urinary follicle stimulating hormone. The small comparative trial, while not sufficiently powered to be considered a formal equivalence trial, suggested that the two recombinant DNA technology compounds require a similar total dose and a similar length of treatment to achieve pre-ovulatory conditions. Although the clinical trial data was derived exclusively from studies in the indication ovarian stimulation, the information is relevant to the posology of GONAL-f in all indications. Section 4.2 in the SPC was updated accordingly (positive CPMP opinion on 25 February 1999).

Anovulation in women who have been unresponsive to treatment with clomiphene citrate.(i)

Although the same pharmacological activity of GONAL-f (stimulation of follicular development) is relevant to the WHO group II anovulatory indication, the clinical data relating to this indication was submitted after the authorisation of GONAL-f as a Type II Variation, for the inclusion of this new indication.

A new clinical study GF 5642, was submitted by the company in support of this new indication. This study compared the efficacy and safety of GONAL-f given subcutaneously, to Metrodin given intramuscularly in patients with WHO type II anovulation, who have failed to ovulate or conceive during previous therapy with clomiphene citrate. Study GF 5642 was an open, randomized, parallel group study, where the patient population was chosen appropriately for this indication. Two hundred and twenty two patients entered treatment; 110 receiving GONAL-f and 112 receiving Metrodin. The study continued for 3 cycles.

The results from this study showed that the cumulative ovulation rate was 84% for the GONAL-f group and 91% for the Metrodin group: the difference was not statistically significant. No difference in secondary variables was observed except for oestradiol levels which were higher (during certain cycles) in the Metrodin group and FSH levels which were greater for GONAL-f (during certain cycles).

Indication in women with severe LH and FSH deficiency. (iii)

The Marketing Authorisation Holder applied for the extension of the indication to include FSH and LH deficient females "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 clinical trials these patients were defined by an endogenous serum LH level <1.2 IU/l."

Co-administration of GONAL-f and r-hLH does not modify their respective pharmacokinetic characteristics.

Three phase II/III studies, one European pivotal (n=38) and two supportive in the US and Spain (n=40, n=38), were completed at the time of application. The number of patients enrolled in the studies was considered sufficient, considering the rarity of the condition. The studies were designed primarily to determine the minimum effective dose and assess the safety of r-hLH to support r-hFSH- induced follicular development in LH and FSH deficient anovulatory women. The dose of 150 IU FSH was chosen based on clinical experience showing that most patients respond to <150 IU FSH. The results also indicate that r-hLH increases ovarian sensitivity to r-hFSH and that a conservative starting dose of r-hFSH should be chosen. The dosing recommendations for GONAL-f proposed in the SPC are in line with clinical practice rather than the posology used in the clinical trial. The risk-benefit of the concomitant use of r-hFSH and r-hLH in the treatment of anovulatory women with severe LH and FSH deficiency was judged to be favourable and to meet the requirements for the addition of a new indication.

Male hypogonadotropic hypogonadism. (iv)

For this extension of the indications the MAH has presented results of two phase III, multinational, multicentre, non-comparative, uncontrolled open clinical studies, one pivotal (GF 5844) and one supportive (GF 6410). Both studies had the same objectives, to determine whether subcutaneous GONAL-f in combination with hCG (human chorionic gonadotrophin, Profasi) would initiate spermatogenesis, achieving sperm counts of at least $1.5 \times 10^6/\text{ml}$, and whether administration of GONAL-f subcutaneously for 18 months in combination with Profasi was safe and tolerable.

Patients received a pre-treatment with Profasi for up to 6 months, with adjustment of the dose to maintain testosterone concentrations at an adequate concentration. Patients who had adequate serum testosterone concentrations and who remained azoospermic proceeded to the treatment phase of the study. For treatment patients received 150 IU GONAL-f by subcutaneous injection into the anterior abdominal wall three times a week. The dose was increased to 225 IU three times a week (pivotal study) and up to 150 IU daily (supportive study) if the response was poor. A dose of at least 2000 IU Profasi was administered twice a week either intramuscularly or subcutaneously. Treatment was continued for 18 months.

In the pivotal study, 12/19 (63%) patients achieved the primary endpoint (sperm counts of at least $1.5 \times 10^6/\text{ml}$), 3/19 (16%) achieved counts of less than $1.5 \times 10^6/\text{ml}$ but greater than $1.0 \times 10^6/\text{ml}$, and 4/19 (21%) remained azoospermic. Of the 7 couples wishing to conceive, 6 pregnancies occurred in the partners of 4 patients, of which 5 went to term, with vaginal delivery of healthy babies. In the supportive study, 5/8 (62.5%) patients achieved the primary endpoint (sperm counts of at least $1.5 \times 10^6/\text{ml}$), 2/8 (25%) achieved counts less than $1.5 \times 10^6/\text{ml}$ but greater than 0, and 1/8 (12.5%) remained azoospermic. Two pregnancies occurred, with vaginal delivery of healthy babies.

Although both clinical trials involved a limited number of patients, given that male congenital or acquired hypogonadotropic hypogonadism is already an approved indication for highly purified urinary derived follicle stimulating hormone, and given the rarity of the disease, the submitted documentation was considered sufficient.

During the assessment of the application for the new indication, it was noted that the posology instructions do not include pre-treatment with hCG as used in the clinical studies. Since concomitant treatment with hCG can also be started without pre-treatment and this is common practice, supported by clinical studies, with urinary follicle stimulating hormone, the MAH did not wish to appear to be suggesting a different management approach for the two types of follicle stimulating hormone.

Safety

The adverse events profile of FSH preparations often related to ovarian stimulation. These adverse events were mostly non-serious (ovarian cysts) and reflected also the efficacy of the preparation.

Although no reports of hypersensitivity to GONAL-f have been reported this was felt to be a theoretical risk in patients with a prior history of hypersensitivity to gonadotropin preparations. The SPC has therefore been modified to say that the first injection of GONAL-f in such patients must be

performed under direct medical supervision, with full cardio-pulmonary resuscitation facilities immediately available.

Local injection site reactions were more common in the GONAL-f group than in the Metrodin group (23% vs 14% moderate/severe reactions respectively). Analysis of the data demonstrated the differences were small and generally not statistically significant, and were, at least in part, due to the different route of administration of the two medicinal products (SC vs IM).

The frequency and severity of the reactions decreased markedly after the first few days of treatment. In view of these findings additional information on injection site reactions was added to the SPC, together with a statement that self-injection should only be recommended in adequately trained, well-motivated patients with access to expert advice.

In study GF 5642, two serious adverse events were observed with GONAL-f; 1 major malformation and 1 miscarriage. Ovarian cysts were also observed in both treatment groups (GONAL-f (4) and Metrodin (6)). The risk of developing ovarian hyperstimulation syndrome (OHSS), as proportion of the cycles in the total treated population was observed to be 3.6% for GONAL-f treated patients and 5.7% for Metrodin treated patients. No cases of thrombotic events or deaths were reported in this study. The CPMP concluded that the benefit/risk balance was comparable for the two medicinal products, GONAL-f and Metrodin.

In female patients, the majority of adverse events observed are ovarian hyperstimulation (or its complications), injection site reactions, GI disturbances, headache and very rarely mild systemic allergy and thromboembolism. Rarely, complications of OHSS, for example ovarian torsion have been seen. In section 4.4 of the SPC other complications of severe OHSS, such as ascites as well as mild systemic allergic reactions such as erythema, rash or facial swelling.

Safety in men

In men common undesirable effects are gynecomastia, acne and weight gain.

No deaths were reported in clinical trials. In the pivotal study four serious adverse events were reported: increased testicular size and cryptorchidism, haemoptysis, infected pilonidal sinus and lymphadenopathy caused by Epstein-Barr virus. Among other adverse events, those considered probably or possibly related to the study medication were varicocele (4 patients), acne (2), gynaecomastia (1), local reactions (3), headache (1), elevated liver function tests (1).

Since no follow up information after the termination of the clinical study were provided, the Marketing Authorisation Holder will provide data from long-term follow up of patients entered in the clinical trials as a post approval commitment.

5. Overall conclusions and benefit/risk assessment

The CPMP considered that the pivotal study in IVF-ET adequately supported use of GONAL-f in Assisted Reproductive Technologies. It was recommended that the indication WHO Group II anovulation be withheld pending provision of further data. Deletion of the intramuscular route of administration was recommended.

The CPMP during its meeting of 16-17 May 1995 discussed the texts of the SPC, Labels and Package Leaflets and adopted by consensus four separate favourable opinions on granting Marketing Authorisations to GONAL-f in the European Union.

The conclusions are reflected in the final versions of the SPC, package leaflet and labelling. As it is proposed that GONAL-f may be self-administered, the Rapporteurs and the CPMP requested that the package leaflet be revised to include diagrams and instructions on self-administration. The Package leaflet was revised accordingly.

On the basis of a new study (study 5642), on the safety and efficacy of GONAL-f in patients with anovulation who failed to ovulate or conceive during previous clomiphene citrate therapy, the CPMP during its meeting on 13-15 February 1996, agreed to include this extension to the indication. The new information led to changes in the SPC as well as the package leaflet. The proposed amendments to the SPC and Package Leaflets were also adopted during the February CPMP meeting.

On 25 February 1999 the CPMP adopted three positive opinions:

- the first for the use of GONAL-f in men affected by hypogonadotropic hypogonadism on the basis of new toxicological and clinical studies and because this new indication had already been approved, with the same posology, for urinary follicle stimulating hormone;
- the second for updating the SPC, Package Leaflet and Labelling according to new scientific information. A major change concerning the relative potency of GONAL-f compared to urinary FSH was introduced in Section 4.2 of the SPC;
- the third for the addition of a new strength: GONAL-f 37.5 IU in ampoules.

On 21 September 2000, the CPMP adopted a positive opinion for GONAL-f 600 IU/ml (multidose) and on 1 March 2001 the CPMP approved a new indication: 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 clinical trials these patients were defined by an endogenous serum LH level <1.2 IU/l.

On the same date (21 September 2000), the CPMP was of the opinion that the quality, the safety and the efficacy of this medicinal product continued to be adequately and sufficiently demonstrated and therefore considered that the benefit/risk profile of GONAL-f continued to be favourable for the authorised indications and issued on 21 September 2000 a positive opinion for the first Renewal of the Marketing Authorisation.

On 13 December 2001, the CPMP adopted 2 positive opinions for GONAL-f affecting the product range:

- Change to formulate and fill the medicinal product by mass (based on protein content) rather than by definition of activity (IU) (based on bioassay). As a result, the quantity of active substance and strength are defined in mass units. Based on the provided data, a conversion factor of 75 IU (target bioavailability) to 5.46 micrograms was determined (rounded up to 5.5 micrograms). GONAL-f is dual labelled: mass as the primary unit and International Units. It is considered necessary to include both mass and IU on product information/labels, at least until users are familiarised with the new units.
- Addition of methionine and polysorbate 20 as excipients to the filled by mass monodose presentations with the solvent presented in pre-filled syringes, to improve the stability of the product and to reduce the rate of oxidation

The SPC, Labelling and Package Leaflet were amended accordingly. On 25 September 2003, the CPMP considered that the benefit/risk profile of a new pharmaceutical form for GONAL-f (i.e. solution for injection presented in a pre-filled pen) was favourable. A positive opinion was therefore adopted on the addition of this new pharmaceutical form, a ready-to-use formulation designed to facilitate the administration of the product.

On the same date (25 September 2003), the CPMP adopted a positive opinion for a Type II variation for a new multidose presentation for GONAL-f powder and solvent for solution for injection 300 IU/0.50 ml (22 micrograms/0.50ml). After reconstitution with 0.75 ml of solvent, its concentration is the same as for the already authorised multidose presentations i.e. 600 IU/ml.