SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<TRADE NAME> <STRENGTH> Solution for Injection

<REGARDING THE APPROVAL>

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains <STRENGTH> of follitropin alfa.

Excipient with known effect:

<REGARDING THE APPROVAL>

For the full list of excipients, see section 6.1.

1. PHARMACEUTICAL FORM

Solution for Injection

<REGARDING THE APPROVAL>

1. CLINICAL PARTICULARS
	1. Therapeutic indications

In adult women

* Anovulation (including polycystic ovarian syndrome) in women who have been unresponsive to treatment with clomifene citrate.
* Stimulation of multifollicular development in women undergoing superovulation for assisted reproductive technologies (ART) such as in vitro fertilisation (IVF), gamete intra-fallopian transfer and zygote intra-fallopian transfer.
* Follitropin alfa in association with a luteinising hormone (LH) preparation is indicated for the stimulation of follicular development in women with severe LH and FSH deficiency.

In adult men

* Follitropin alfa is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotropic hypogonadism with concomitant human Chorionic Gonadotropin (hCG) therapy.
	1. Posology and method of administration

Treatment with follitropin alfa should be initiated under the supervision of a physician experienced in the treatment of fertility disorders.

Posology

The dose recommendations given for follitropin alfa are those in use for urinary FSH. Clinical assessment of follitropin alfa indicates that its daily doses, regimens of administration and treatment monitoring procedures should not be different from those currently used for urinary FSH-containing medicinal products. It is advised to adhere to the recommended starting doses indicated below.

Comparative clinical studies have shown that on average patients require a lower cumulative dose and shorter treatment duration with follitropin alfa compared with urinary FSH. Therefore, it is considered appropriate to give a lower total dose of follitropin alfa than generally used for urinary FSH, not only in order to optimise follicular development but also to minimise the risk of unwanted ovarian hyperstimulation (see section 5.1).

*Women with anovulation (including polycystic ovarian syndrome)*

Follitropin alfa may be given as a course of daily injections. In menstruating women treatment should commence within the first 7 days of the menstrual cycle.

A commonly used regimen commences at 75 to 150 IU FSH daily and is increased preferably by 37.5 or 75 IU at 7- or preferably 14-day intervals if necessary, to obtain an adequate, but not excessive, response. Treatment should be tailored to the individual patient’s response as assessed by measuring follicle size by ultrasound and/or estrogen secretion. The maximal daily dose is usually not higher than 225 IU FSH. If a patient fails to respond adequately after 4 weeks of treatment, that cycle should be abandoned and the patient should undergo further evaluation after which she may recommence treatment at a higher starting dose than in the abandoned cycle.

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

If an excessive response is obtained, treatment should be stopped and hCG withheld (see section 4.4). Treatment should recommence in the next cycle at a dose lower than that of the previous cycle.

*Women undergoing ovarian stimulation for multiple follicular development prior to in vitro fertilisation or other ART*

A commonly used regimen for superovulation involves the administration of 150 to 225 IU of follitropin alfa 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 estrogen concentrations and/or ultrasound examination), with the dose adjusted according to the patient’s response, to usually not higher than 450 IU daily. In general adequate follicular development is achieved on average by the tenth day of treatment (range 5 to 20 days).

A single injection of 250 micrograms r-hCG or 5 000 IU up to 10 000 IU hCG is administered 24 to 48 hours after the last follitropin alfa injection to induce final follicular maturation.

Down-regulation with a gonadotropin-releasing hormone (GnRH) agonist or antagonist is now commonly used in order to suppress the endogenous LH surge and to control tonic levels of LH. In a commonly used protocol, follitropin alfa is started approximately 2 weeks after the start of agonist treatment, both being continued until adequate follicular development is achieved. For example, following two weeks of treatment with an agonist, 150 to 225 IU follitropin alfa are administered for the first 7 days. The dose is then adjusted according to the ovarian response.

Overall experience with IVF indicates that in general the treatment success rate remains stable during the first four attempts and gradually declines thereafter.

*Women with severe LH and FSH deficiency*

In LH and FSH deficient women, the objective of follitropin alfa therapy in association with a luteinising hormone (LH) preparation is to promote follicular development followed by final maturation after the administration of hCG. Follitropin alfa should be given as a course of daily injections simultaneously with lutropin alfa. If the patient is amenorrhoeic and has low endogenous estrogen secretion, treatment can commence at any time.

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

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

When an optimal response is obtained, a single injection of 250 micrograms r-hCG or 5 000 IU up to 10 000 IU hCG should be administered 24 to 48 hours after the last follitropin alfa and lutropin alfa injections. The patient is recommended to have coitus on the day of, and on the day following, hCG administration. Alternatively, intrauterine insemination or another medically assisted reproduction procedure may be performed based on the physician’s judgment of the clinical case.

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

If an excessive response is obtained, treatment should be stopped and hCG withheld. Treatment should recommence in the next cycle at a dose of FSH lower than that of the previous cycle (see section 4.4).

*Men with hypogonadotropic hypogonadism*

Follitropin alfa should be given at a dose of 150 IU three times a week, concomitantly with hCG, for a minimum of 4 months. If after this period, the patient has not responded, the combination treatment may be continued; current clinical experience indicates that treatment for at least 18 months may be necessary to achieve spermatogenesis.

*Special population*

Elderly population

There is no relevant use of follitropin alfa in the elderly population. Safety and efficacy of follitropin alfa in elderly patients have not been established.

Renal or hepatic impairment

Safety, efficacy and pharmacokinetics of follitropin alfa in patients with renal or hepatic impairment have not been established.

Paediatric population

There is no relevant use of follitropin alfa in the paediatric population.

*Method of administration*

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

As the multidose cartridge is intended for several injections, clear instructions should be provided to the patients to avoid misuse of the medicine.

Follitropin alfa cartridge is designed for use in conjunction with thef follitropin alfa pen only, which is separately available. For instructions on the administration with the follitropin alfa pen, see section 6.6. <REGARDING THE APPROVAL>

* 1. Contraindications
	+ Hypersensitivity to the active substance follitropin alfa, FSH or to any of the excipients listed in section 6.1;
	+ tumours of the hypothalamus or pituitary gland;
	+ ovarian enlargement or ovarian cyst unrelated to polycystic ovarian disease and of unknown origin;
	+ gynaecological haemorrhages of unknown origin;
	+ ovarian, uterine or mammary carcinoma.

Follitropin alfa must not be used when an effective response cannot be obtained, such as:

* + primary ovarian failure;
	+ malformations of sexual organs incompatible with pregnancy;
	+ fibroid tumours of the uterus incompatible with pregnancy;
	+ primary testicular insufficiency.
	1. Special warnings and precautions for use

*Traceability*

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

*General*

Follitropin alfa is a potent gonadotropic substance capable of causing mild to severe adverse reactions and should only be used by physicians who are thoroughly familiar with infertility problems and their management.

Gonadotropin therapy requires a certain time commitment by physicians and supportive health care professionals, as well as the availability of appropriate monitoring facilities. In women, safe and effective use of follitropin alfa calls for monitoring of ovarian response with ultrasound, alone or preferably in combination with measurement of serum estradiol levels, on a regular basis. There may be a degree of interpatient variability in response to FSH administration, with a poor response to FSH in some patients and exaggerated response in others. The lowest effective dose in relation to the treatment objective should be used in both men and women.

*Porphyria*

Patients with porphyria or a family history of porphyria should be closely monitored during treatment with follitropin alfa. Deterioration or a first appearance of this condition may require cessation of treatment.

*Treatment in women*

Before starting treatment, the couple’s infertility should be assessed as appropriate and putative contraindications for pregnancy evaluated. In particular, patients should be evaluated for hypothyroidism, adrenocortical deficiency, hyperprolactinemia and appropriate specific treatment given.

Patients undergoing stimulation of follicular growth, whether as treatment for anovulatory infertility or ART procedures, may experience ovarian enlargement or develop hyperstimulation. Adherence to recommended follitropin alfa dose and regimen of administration and careful monitoring of therapy will minimise the incidence of such events. For accurate interpretation of the indices of follicle development and maturation, the physician should be experienced in the interpretation of the relevant tests.

In clinical trials, an increase of the ovarian sensitivity to follitropin alfa was shown when administered with lutropin alfa. If an FSH dose increase is deemed appropriate, dose adaptation should preferably be at 7 to 14 day intervals and preferably with 37.5 to 75 IU increments.

No direct comparison of follitropin alfa/LH versus human menopausal gonadotropin (hMG) has been performed. Comparison with historical data suggests that the ovulation rate obtained with follitropin alfa/LH is similar to that obtained with hMG.

*Ovarian Hyperstimulation Syndrome (OHSS)*

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

In distinction to uncomplicated ovarian enlargement, OHSS is a condition that can manifest itself with increasing degrees of severity. It comprises marked ovarian enlargement, high serum sex steroids and an increase in vascular permeability which can result in an accumulation of fluid in the peritoneal, pleural and, rarely, in the pericardial cavities.

The following symptomatology may be observed in severe cases of OHSS: abdominal pain, abdominal distension, severe ovarian enlargement, weight gain, dyspnoea, oliguria and gastrointestinal symptoms including nausea, vomiting and diarrhoea. Clinical evaluation may reveal hypovolaemia, haemoconcentration, electrolyte imbalances, ascites, haemoperitoneum, pleural effusions, hydrothorax, or acute pulmonary distress. 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 include young age, lean body mass, polycystic ovarian syndrome, higher doses of exogenous gonadotropins, high absolute or rapidly rising serum estradiol levels and previous episodes of OHSS, large number of developing ovarian follicles and large number of oocytes retrieved in assisted reproductive technology (ART) cycles.

Adherence to recommended follitropin alfa dose and regimen of administration can minimise the risk of ovarian hyperstimulation (see sections 4.2 and 4.8). Monitoring of stimulation cycles by ultrasound scans as well as estradiol measurements are recommended to early identify risk factors.

There is evidence to suggest that hCG plays a key role in triggering OHSS and that the syndrome may be more severe and more protracted if pregnancy occurs. Therefore, if signs of ovarian hyperstimulation occur such as serum estradiol level > 5,500 pg/mL or > 20,200 pmol/L and/or ≥ 40 follicles in total, it is recommended that hCG be withheld and the patient be advised to refrain from coitus or to use barrier contraceptive methods for at least

4 days. OHSS may progress rapidly (within 24 hours) or over several days to become a serious medical event. It most often occurs after hormonal treatment has been discontinued and reaches its maximum at about 7 to 10 days following treatment. Therefore, patients should be followed for at least 2 weeks after hCG administration.

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

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

*Multiple pregnancy*

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

To minimise the risk of multiple pregnancy, careful monitoring of ovarian response is recommended.

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

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

*Pregnancy loss*

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

*Ectopic pregnancy*

Women with a history of tubal disease are at risk of ectopic pregnancy, whether the pregnancy is obtained by spontaneous conception or with fertility treatments. The prevalence of ectopic pregnancy after ART, was reported to be higher than in the general population.

*Reproductive system neoplasms*

There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple treatment regimens for infertility treatment. It is not yet established whether or not treatment with gonadotropins increases the risk of these tumours in infertile women.

*Congenital malformation*

The prevalence of congenital malformations after ART may be slightly higher than after spontaneous conceptions. This is thought to be due to differences in parental characteristics (e.g. maternal age, sperm characteristics) and multiple pregnancies.

*Thromboembolic events*

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

*Treatment in men*

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

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

*Benzalkonium chloride content*

Follitropin alfa contains 0.02 mg/mL of benzalkonium chloride <REGARDING THE APPROVAL>

*Benzyl alcohol content*

Follitropin alfa contains 10.0 mg per mL benzyl alcohol

Benzyl alcohol may cause allergic reactions.

High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment as well as in pregnant women or while breast-feeding, because of the risk of accumulation and toxicity (metabolic acidosis). <REGARDING THE APPROVAL>

*Sodium content*

Follitropin alfa contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially “sodiumfree”. <REGARDING THE APPROVAL>

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* 1. Interaction with other medicinal products and other forms of interaction

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

* 1. Fertility, pregnancy and lactation

*Pregnancy*

There is no indication for use of follitropin alfa during pregnancy. Data on a limited number of exposed pregnancies (less than 300 pregnancy outcomes) indicate no malformative or foeto/neonatal toxicity of follitropin alfa.

No teratogenic effect has been observed in animal studies (see section 5.3). In case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of follitropin alfa.

*Breast-feeding*

Follitropin alfa is not indicated during breast-feeding.

*Fertility*

Follitropin alfa is indicated for use in infertility (see section 4.1)..

* 1. Effects on ability to drive and use machines

Follitropin alfa has no or negligible influence on the ability to drive and use machines.

* 1. Undesirable effects

*Summary of the safety profile*

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

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

Thromboembolism may occur very rarely (see section 4.4).

*Tabulated list of adverse reactions*

The adverse reactions are ranked under heading of frequency using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

*Treatment in women*

**Table 1: Adverse reactions in women**

| **System organ class** | **Frequency** | **Adverse reaction** |
| --- | --- | --- |
| Immune system disorders | Very rare | Mild to severe hypersensitivity reactions, including anaphylactic reactions and shock |
| Nervous system disorders | Very common | Headache |
| Vascular disorders | Very rare | Thromboembolism (both in association with and separate from OHSS) |
| Respiratory, thoracic and mediastinal disorders | Very rare | Exacerbation or aggravation of asthma |
| Gastrointestinal disorders | Common | Abdominal pain, abdominal distension, abdominal discomfort, nausea, vomiting, diarrhoea |
| Reproductive system and breast disorders | Very common | Ovarian cysts |
| Common | Mild or moderate OHSS (including associated symptomatology) |
| Uncommon | Severe OHSS (including associated symptomatology) (see section 4.4) |
| Rare | Complication of severe OHSS |
| General disorders and administration site conditions | Very common | Injection site reactions (e.g. pain, erythema, haematoma, swelling and/or irritation at the site of injection) |

*Treatment in men*

**Table 2: Adverse reactions in men**

|  |  |  |
| --- | --- | --- |
| **System organ class** | **Frequency** | **Adverse reaction** |
| 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 |
| Skin and subcutaneous tissue disorders | Common | Acne |
| Reproductive system and breast disorders | Common | Gynaecomastia, varicocele  |
| General disorders and administration site conditions | Very common | Injection site reactions (e.g. pain, erythema, haematoma, swelling and/or irritation at the site of injection) |
| Investigations | Common | Weight gain |

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Health Product Vigilance Center; HPVC

* 1. Overdose

The effects of an overdose of follitropin alfa are unknown, nevertheless, there is a possibility that OHSS may occur (see section 4.4).

1. PHARMACOLOGICAL PROPERTIES
	1. Pharmacodynamic properties

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

Follitropin alfa is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency http://www.ema.europa.eu.

Mechanism of action

Follicle stimulating hormone (FSH) and luteinising hormone (LH) are secreted from the anterior pituitary gland in response to GnRH and play a complementary role in follicle

development and ovulation. FSH stimulates the development of ovarian follicles, while LH action is involved in follicle development, steroidogenesis and maturation.

Pharmacodynamic effects

Inhibin and estradiol (E2) levels are raised after administration of r-hFSH, with subsequent induction of follicular development. Inhibin serum level increase is rapid and can be observed as early as the third day of r-hFSH administration, while E2 levels take more time, and an increase is observed only from the fourth day of treatment. Total follicular volume starts to increase after 4 to 5 days of r-hFSH daily dosing, and, depending on patient response, the maximum effect is reached after about 10 days from the start of r-hFSH administration.

Clinical efficacy and safety in women

In clinical trials, patients with severe FSH and LH deficiency were defined by an endogenous serum LH level < 1.2 IU/L as measured in a central laboratory. However, it should be taken into account that there are variations between LH measurements performed in different laboratories.

In clinical studies comparing r-hFSH (follitropin alfa) and urinary FSH in ART (see table 3 below) and in ovulation induction, follitropin alfa was more potent than urinary FSH in terms of a lower total dose and a shorter treatment period needed to trigger follicular maturation.

In ART, follitropin alfa at a lower total dose and shorter treatment period than urinary FSH, resulted in a higher number of oocytes retrieved when compared to urinary FSH.

Table 3: Results of study GF 8407 (randomised parallel group study comparing efficacy and safety of follitropin alfa with urinary FSH in ART).

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

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

*Clinical efficacy and safety in men*

In men deficient in FSH, follitropin alfa administered concomitantly with hCG for at least 4 months induces spermatogenesis.

* 1. Pharmacokinetic properties

After There is no pharmacokinetic interaction between follitropin alfa and lutropin alfa when administered simultaneously.

*Distribution*

Following intravenous administration, follitropin alfa is distributed to the extracellular fluid space with an initial half-life of around 2 hours and eliminated from the body with a terminal half-life of 14 to 17 hours. The steady state volume of distribution is in the range of 9 to 11 L.

Following subcutaneous administration, the absolute bioavailability is 66% and the apparent terminal half-life is in the range of 24 to 59 hours. Dose proportionality after subcutaneous administration was demonstrated up to 900 IU. Following repeated administration, follitropin alfa accumulates 3-fold achieving a steady-state within 3 to 4 days.

*Elimination*

Total clearance is 0.6 L/h and about 12% of the follitropin alfa dose is excreted in the urine..

* 1. Preclinical safety data

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

Impaired fertility has been reported in rats exposed to pharmacological doses of follitropin alfa (≥ 40 IU/kg/day) for extended periods, through reduced fecundity.

Given in high doses (≥ 5 IU/kg/day) follitropin alfa caused a decrease in the number of viable foetuses without being a teratogen and dystocia similar to that observed with urinary menopausal gonadotropin (hMG). However, since follitropin alfa is not indicated in pregnancy, these data are of limited clinical relevance.

1. PHARMACEUTICAL PARTICULARS
	1. List of excipients

<REGARDING THE APPROVAL>

* 1. Incompatibilities

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

* 1. Shelf life

<REGARDING THE APPROVAL>

* 1. Special precautions for storage

<REGARDING THE APPROVAL>

* 1. Nature and contents of container

<REGARDING THE APPROVAL>

* 1. Special precautions for disposal

<REGARDING THE APPROVAL>

1. MARKETING AUTHORISATION HOLDER

<REGARDING THE APPROVAL>

1. MARKETING AUTHORISATION NUMBER(S)

<REGARDING THE APPROVAL>

1. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<REGARDING THE APPROVAL>

1. DATE OF REVISION OF THE TEXT1

<REGARDING THE APPROVAL>