SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product:

Recombinant human follicle stimulating hormone (follitropin alfa) solution for injection in prefilled syringe and vial

2. Qualitative and Quantitative Composition

Each prefilled syringe contains 75 IU (equivalent to 5.5 mcg) of follitropin alfa* in 0.12 ml solution for injection.

Each multiple use vial contains 1200 IU (equivalent to 88 mcg) of follitropin alfa* in 1.92 ml solution for injection.

*Recombinant human follitropin alfa (r-hFSH) is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form:

Clear and colorless solution for injection.

4. Clinical Particulars

4.1. Therapeutic indications

In adult women

- Anovulation (including polycystic ovarian syndrome) in women who have been unresponsive to treatment with clomiphene citrate.
- Stimulation of 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 luteinising hormone (LH) preparation is recommended for the stimulation of follicular development in women with severe LH and FSH deficiency.

In adult men

4.2. Follitropin alfa is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism with concomitant human chorionic gonadotrophin (hCG) therapy.**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.

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 fertilization or other assisted reproductive technologies

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 luteinising hormone (LH) preparation is to promote follicular development followed by final maturation after the administration of human chorionic gonadotropin (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 luteotrophic activity (LH/hCG) after ovulation may lead to premature failure of the corpus luteum.

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

Men with hypogonadotrophic hypogonadism

Follitropin alfa (r-Hu FSH) 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 populations

Elderly

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 injection should be given at the same time each day.

The first injection of follitropin alfa should be performed under direct medical supervision. Self-administration of follitropin alfa should only be performed by patients who are well motivated, adequately trained and have access to expert advice.

The injection site should be alternated daily.

For instructions on reconstitution of the medicinal product see section 6.6 and the package leaflet.

4.3. Contraindications

- hypersensitivity to the active substance 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

4.4. Special warnings and precautions for use

Traceability

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

General recommendations

Follitropin alfa 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.

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 inter-patient variability in response to FSH administration, with a poor response to FSH in some patients and exaggerated response in others. The lowest effective dose in relation to the treatment objective should be used in both men and women.

Porphyria

Patients with porphyria or a family history of porphyria should be closely monitored during treatment with 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. 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 seven to ten days following treatment. Therefore, patients should be followed for at least two weeks after hCG administration.

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

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

Multiple pregnancy

In patients undergoing 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.

4.5. Interaction with other medicinal products and other forms of interactions

Concomitant use of follitropin alfa with other medicinal productsused to stimulate ovulation (e.g. hCG, clomiphene citrate) may potentiate the follicular response, whereas concurrent use of a GnRH agonist or antagonist to induce pituitary desensitization 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.

4.6. 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 feto/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).

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

Summary of the safety profile

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

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

Thromboembolism may occur very rarely (see section 4.4).

List of adverse reactions

The following definitions apply to the frequency terminology used hereafter: 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).

Treatment in women

Immune system disorders	
Very rare	Mild to severe hypersensitivity reactions including anaphylactic reactions and shock
Nervous system disorders	
Very common	Headache
Vascular disorders	
Very rare	Thromboembolism (both in association with and separate from OHSS)
Respiratory, thoracic and mediastinal disorders	
Very rare	Exacerbation or aggravation of asthma
Gastrointestinal disorders	
Common	Abdominal pain, abdominal distension, abdominal discomfort, nausea, vomiting, diarrhoea
Reproductive system and breast disorders	
Very common	Ovarian cysts
Common	Mild or moderate OHSS (including associated symptomatology)
Uncommon	Severe OHSS (including associated symptomatology) (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

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

4.9. Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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

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 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: Results of a randomised parallel group study comparing efficacy and safety of follitropin alfa with urinary FSH in assisted reproduction technologies

	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.

5.2 Pharmacokinetic Properties

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 about 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 about 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.

5.3 Preclinical safety Data

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

Preclinical toxicity studies of follitropin alfa were conducted in rodents (mice and rat) and non-rodents (New Zealand white rabbit and Guinea pig). Acute toxicity studies were conducted on mice and rat. In case of acute toxicity studies the drug was administered by intravenous and subcutaneous routes**.** The results of acute toxicity demonstrate that follitropin alfa is safe at the doses 30 times higher than the recommended human dose (0.55 mcg/kg).

In Subacute toxicity studies (with and without recovery) in two species (rats and rabbits) with subcutaneous route, all the animals showed normal hematology, biochemistry and histopathology of vital organs suggesting that follitropin alfa is safe at the doses as high as 30 times than the recommended human dose (0.55 mcg/kg).

Follitropin alfa was also evaluated for local irritation by acute dermal irritation test in New Zealand white rabbits (Draize test) and Skin Sensitization Test in Dunkin Hartley Guinea Pigs. The results of local irritation test with the test drug did not show any irritation or edema at the site of application in rabbits. The result of skin sensitization test did not show any dermal response or allergenicity at the site of application in Guinea pigs.

6. Pharmaceutical Particulars

6.1 List of Excipients

- Monosodium dihydrogen phosphate monohydrate
- Di sodium hydrogen phosphate dihydrate
- Sodium Chloride
- Polysorbate 20
- Mannitol
- L-Methionine
- Trehalose dihydrate
- Ortho phosphoric acid**

- Sodium hydroxide**
- Water for injection

**For pH adjustment

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life 2 years from the date of manufacture.

6.4 Special precautions for storage

Store at 2 °C-8 °C (in a refrigerator). Do not freeze or shake. Keep out of reach and sight of children. The solution should not be administered if it contains particles or is not clear.

6.5 Nature and contents of container

Each prefilled syringe (USP type I glass) contains a rubber stopper, stainless steel needle and needle cap.

Each multiple-use vial (USP type I glass) contains rubber stopper and seal with plastic flip. Vial is placed in a plastic tray and packed in a carton.

6.6 Special precautions for disposal and other handling

For single use only.

Prior to subcutaneous administration and if the prefilled syringe or vial is kept refrigerated, it should be allowed to sit at room temperature for at least 30 minutes before injecting to allow the medicinal product to reach room temperature. The prefilled syringe or vial must not be warmed by using a microwave or other heating element.

The solution should not be administered if it contains particles or is not clear.

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

7 Marketing Authorization Holder

Not Applicable

8 Marketing Authorization Number(s):

Not Applicable

9 Date of First Authorisation / Renewal of the Authorisation :

Not Applicable

10 Date of Revision of the text

Not applicable