1.5 PRODUCT INFORMATION

1.5.1 Summary of Product Characteristics, Labeling and Package Leaflet

1.5.1.1 Summary of Product Characteristics

1. Name of the Medicinal Product:

Recombinant Human Follicle Stimulating Hormone (follitropin alfa) is available in the strength of 1200 IU/1.92 mL mL in vial as solution for injection.

2. Qualitative and Quantitative Composition

Recombinant Human Follicle Stimulating Hormone (Follitropin Alfa or rHu FSH) Injection: Each mL of solution contains 625 IU (equivalent to 45.8 micrograms) of follitropin alfa*.

Each vial of 1.92 mL contains 1200 IU (equivalent to 88 micrograms) of recombinant human Follicle Stimulating Hormone.

***Recombinant Human Follitropin alfa (rHu FSH) is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.**

For a full list of excipients, see section 6.1.

3. Pharmaceutical Form:

Clear and colorless solution for injection in vial.

4. Clinical Particulars

4.1. Therapeutic indications

In adult women

Anovulation (including polycystic ovarian disease, PCOD) in women who have been unresponsive to treatment with Clomiphene citrate.

Controlled ovarian hyper stimulation to induce the development of multiple follicles in medically assisted reproduction programmes (eg. In vitro fertilization/embryo transfer (IVF/ET), gamete intra fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI).

In association with 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.

In adult men

It is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism with concomitant human Chorionic Gonadotrophin (hCG) therapy.

4.2. 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.

Women with anovulation (including polycystic ovarian syndrome)

The dose must be individualized. The lowest dose expected to result in good response should be used. Follitropin alfa (r-Hu FSH) injection may be given as a regimen of daily injections. In menstruating women treatment should start within the first 7 days of the menstrual cycle. The individual patient's response is monitored by measuring follicle size by ultrasound and/or oestrogen secretion. A commonly used starting dose is 75-150 IU FSH daily and is increased preferably by 37.5 or 75 IU at 7 or preferably 14 day intervals if required, to obtain an adequate, but not excessive, response. The maximal daily dose is usually 225 IU FSH. If a patient fails to respond adequately after 4 weeks of treatment, that cycle should be abandoned. 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 24-48 hours after the last follitropin alfa (r-Hu FSH) injection. The patient is recommended to have coitus on the day of, and the day following, hCG administration. Alternatively intrauterine insemination (IUI) may be performed. If an excessive response is obtained, treatment should be stopped and hCG withheld. Treatment should restart 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

The dosage regimen may vary according to the patient's response. The treatment is started on days 2 or 3 of the cycle. In a commonly used regimen for superovulation, 150-225 IU of follitropin alfa (r-Hu FSH) injection are administered daily, from days 2 or 3 of the cycle. Treatment is continued until adequate follicular development has been achieved. The follicular development is assessed by monitoring of serum oestrogen concentrations and/or ultrasound examination. The dose is 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). In patients undergoing ART, down-regulation with a gonadotrophin-releasing hormone (GnRH) agonist or antagonist is commonly used in order to suppress the endogenous LH surge. In a commonly used protocol, follitropin alfa (r-Hu FSH) is started approximately 2 weeks after the start of agonist treatment, both being continued until adequate follicular development is achieved. Following two weeks of treatment with an agonist, 150-225 IU follitropin alfa (r-Hu FSH) injection are administered for the first 7 days. The dose is then adjusted according to the ovarian response. Subsequently dosage should be adjusted no more frequently than every 3-5 days and by no more than 75-150 IU additionally at each adjustment. Final follicular maturation is induced by administration of single injection of 250 micrograms r-hCG or 5,000 IU up to 10,000 IU hCG 24-48 hours after the last follitropin alfa (r-Hu FSH) injection.

Women with anovulation resulting from severe LH and FSH deficiency:

The objective of follitropin alfa (r-Hu FSH) therapy in association with lutropin alfa in LH and FSH deficient women (hypogonadotrophic hypogonadism), is to develop a single mature Graafian follicle from which the oocyte will be liberated after the administration of human chorionic gonadotropin (hCG). Follitropin alfa (r-Hu FSH) should be given as a course of daily injections simultaneously with lutropin alfa. These patients are amenorrheic and have low endogenous oestrogen secretion. Therefore treatment can commence at any time. A recommended regimen is to start with 75 IU of lutropin alfa daily with 75-150 IU r-Hu FSH. Treatment should be tailored to the individual patient's response as assessed by follicle size measured by ultrasound and oestrogen response. If an increment in FSH dose is required, dose adaptation should preferably be after 7-14 day intervals and preferably by 37.5-75 IU increments. The duration of stimulation may extend 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 24-48 hours after the last follitropin alfa (r-Hu FSH) 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 (IUI) may be performed. Luteal phase support may be recommended 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 restart 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 (Follitropin alfa (r-Hu FSH) with hCG) may be continued. Treatment for at least 18 months may be necessary to achieve spermatogenesis.

Method of administration

Follitropin alfa (r-Hu FSH) is intended for subcutaneous administration. The first injection of Follitropin alfa (r-Hu FSH) should be administered under direct medical supervision. Self-administration of follitropin alfa (r-Hu FSH) should only be performed by patients who are well motivated, adequately trained and have access to expert advice. Suitable site for subcutaneous administration is in the abdomen around the navel. Change the injection site with each injection.

The solution should not be administered if it contains particles or is not clear. The vial is for single use. The injection of follitropin alfa should be administered using pre-calibrated syringes provided along with vial in the package. As follitropin alfa multiple use vial are intended for several injections, clear instruction should be provided to the patients to avoid misuse of the multi-dose presentation. Any unused solution must be discarded not later than 28 days after first opening. Discard used syringes immediately after injection.

Missed Dose

For patients who miss a dose, it is not recommended to double the next dose. The patient should be reminded to contact the physician monitoring their treatment.

Administration

Follitropin alfa is intended for subcutaneous administration.

4.3. Contraindications

rHu FSH (Follitropin α) is contraindicated in patients who exhibit:

1. Prior hypersensitivity to recombinant FSH preparations or one of their excipients.
2. High levels of FSH indicating primary gonadal failure.
3. Uncontrolled thyroid or adrenal dysfunction.
4. Sex hormone dependent tumors of the reproductive tract and accessory organs.
5. An organic intracranial lesion such as a pituitary tumor.
6. Abnormal uterine bleeding of undetermined origin
7. Ovarian cyst or enlargement of undetermined origin
8. Pregnancy.

4.4. Special warnings and precautions for use

Warnings:

Follitropin alfa should only be used by physicians who are thoroughly familiar with infertility problems and their management. Follitropin alfa is a potent gonadotropic substance capable of causing Ovarian Hyperstimulation Syndrome (OHSS) in women with or without pulmonary or vascular complications. Gonadotropin therapy requires a certain time commitment by physicians and supportive health professionals, and requires the availability of appropriate monitoring facilities. Safe and effective use of follitropin alfa in women requires monitoring of ovarian response with serum estradiol and vaginal ultrasound on a regular basis. The lowest effective dose should be used. Prior to therapy with follitropin alfa, patients should be informed of the duration of treatment and monitoring of their condition that will be required. Possible adverse reactions and the risk of multiple births should also be discussed.

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 pituitary or hypothalamus tumours, and appropriate specific treatment given.

Follitropin alfa (r-Hu FSH) is a potent gonadotrophic substance, which can cause mild to severe adverse reactions. It should only be used by physicians who are thoroughly familiar with infertility facilities. In women, ovarian response should be

monitored with ultrasound, alone or preferably in combination with measurement of serum oestradiol 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 (r-Hu FSH). In case of a first appearance or deterioration of this condition, the treatment with Follitropin alfa should be stopped.

Treatment in women: Before starting treatment, the couple's infertility should be assessed and putative contraindications for pregnancy evaluated. In particular, patients should be evaluated for hypothyroidism, adrenocortical deficiency, hyperprolactinemia and appropriate specific treatment given. For accurate interpretation of the indices of follicle development and maturation, the physician should be experienced in the interpretation of the relevant tests, problems and their management. Gonadotropin therapy requires a certain time commitment by physicians and supportive health professionals, and the availability of appropriate monitoring 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 (r-Hu FSH) dose and regimen of administration and careful monitoring of therapy will minimize the incidence of such events.

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 comparison to uncomplicated ovarian enlargement, OHSS comprises marked ovarian enlargement, high serum sex steroids levels, 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. The risk of ovarian hyperstimulation can be minimized by adherence to recommended dose of Follitropin alfa (r-Hu FSH) and regimen of administration. Monitoring of stimulation cycles by ultrasound scans as well as oestradiol measurements are recommended to early identify risk factors.

Independent risk factors for developing OHSS include polycystic ovarian syndrome high absolute or rapidly rising serum oestradiol levels (e.g. > 900 pg/ml or > 3,300 pmol/L in anovulation; > 3,000 pg/ml or > 11,000 pmol/L in ART) and large number of developing ovarian follicles (e.g. > 3 follicles of ≥ 14 mm in diameter in anovulation; ≥ 20 follicles of ≥ 12 mm in diameter in ART). hCG plays a key role in triggering OHSS and that the

syndrome may be more severe and more protracted if pregnancy occurs. Therefore the administration of hCG must be withheld in cases where the ovaries are abnormally enlarged on the last day of Follitropin alfa therapy 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 hospitalized and appropriate therapy be started.

Multiple pregnancy: To minimise the risk of multiple pregnancy, careful monitoring of ovarian response is recommended. In pregnancies occurring after induction of ovulation with gonadotrophin preparations and in women undergoing assisted reproduction, there is an increased risk of multiple gestations. The patient should be advised of the potential risk of multiple births before starting treatment. 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.

Laboratory Tests: The degree of follicular maturation and the timing of hCG administration can both be determined with the use of transvaginal ultrasonography and serum estradiol levels. It is also useful for minimizing the risk of OHSS and multi-fetal gestations. It is recommended that the number of growing follicles be confirmed using ultrasonography because plasma estrogens do not give an indication of the size or number of follicles. Clinical monitoring for spermatogenesis should be based on Serum testosterone level and Semen analysis. Pregnancy loss: Rates of pregnancy loss in women undergoing assisted reproduction techniques are higher than in the normal population.

Ectopic pregnancy: Since infertile women undergoing assisted reproduction, and particularly IVF, often have tubal abnormalities the incidence of ectopic pregnancies with r-Hu FSH treatment might be increased. Early confirmation of a intrauterine pregnancy is therefore important.

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 incidence 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 gestations. Because of differences in parental characteristics (e.g. maternal age, sperm characteristics) and multiple pregnancies, the prevalence of congenital malformations after ART may be slightly higher than after spontaneous conceptions.

Thromboembolic events: In women with recent or ongoing thromboembolic disease or women with generally recognized 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 (r-Hu FSH) /hCG therapy. 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 drugs used to stimulate ovulation (e.g. hCG, clomiphene citrate) may potentiate the follicular response. Concurrent use of a GnRH agonist or antagonist to induce pituitary desensitization may increase the dose of Follitropin alfa required. No other clinically significant drug interaction has been reported.

4.6. Fertility, Pregnancy and lactation

Fertility: Follitropin alfa (r-Hu FSH) is indicated for use in infertility.

Pregnancy: There is no indication for use of follitropin alfa (r-Hu FSH) during pregnancy. Data on a limited number of exposed pregnancies indicate no malformative or feto/neonatal toxicity of follitropin alfa. In case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of Follitropin alfa (r-Hu FSH).

Breastfeeding/Lactation: Follitropin alfa (r-Hu FSH) is not indicated during breastfeeding.

4.7. Effects on ability to drive and use machines

It is expected to have no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

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.

Thromboembolism may occur very rarely, usually associated with severe OHSS.

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, usually associated with severe OHSS (see section 4.4)
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

Overdosage

Aside from possible ovarian hyperstimulation and multiple gestations there is no information on the consequences of acute overdosage with follitropin alfa.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Gonadotropins And Other Ovulation Stimulants ATC Code: G03GA05.

In women, the most important effect resulting from parenteral administration of FSH is the development of mature Graafian follicles. In women with anovulation, the objective of rHu FSH therapy is to develop single mature Graafian follicle from which the ovum will be liberated after administration of Human Chorionic Gonadotropin (hCG). There is interpatient variability in response to FSH administration.

Recombinant Human Follicle Stimulating Hormone injection has been developed as a "similar biological medicinal product. The chosen reference medicinal product is GONAL-f® which is marketed by Merck Sereno Europe Limited. The formulation for follitropin alfa was established based on knowledge of GONAL-f®'s formulation excipients and concentrations. Follitropin alfa injection is a biosimilar medicinal product. Detailed information is available on the European Medicines Agency website; www.emea.europa.eu

5.2 Pharmacokinetic Properties

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 24 hours. The steady state volume of distribution and total clearance are 10 L and 0.6 L/h, respectively. One-eighth of the follitropin alfa dose is excreted in the urine.

Following subcutaneous administration, the absolute bioavailability is about 70 %. Following repeated administration, follitropin alfa accumulates 3-fold achieving a steady-state within 3-4 days. In women whose endogenous gonadotropin secretion is suppressed, follitropin alfa has nevertheless been shown to effectively stimulate follicular development and steroidogenesis, despite unmeasurable LH levels.

5.3 Preclinical safety Data

Preclinical toxicity studies with rHu FSH are 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 Intas rHu FSH 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 & rabbits) with subcutaneous route, all the animals have shown normal hematology, biochemistry and histopathology of vital organs suggesting that Intas rHu FSH is safe at the doses as high as 30 times than the recommended human dose (0.55 mcg / kg).

Intas rHu FSH 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**
- Phenol
- Water for injection

**For pH adjustment

6.2 Incompatibilities

No evidence of interaction of rHu FSH with other drugs was observed in the course of clinical trials.

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.

After first use, the product may be stored at or below 25 °C for up to 28 days and must be discarded if not used.

6.5 Nature and contents of container

Container closure system for 1200 IU/1.92 mL consists of vial system comprising of 2 mL multiple use USP Type I glass vial, bromobutyl rubber coated with fluororesin rubber stopper and 13 mm flip off aluminium seal.

6.6 Special precautions for disposal and other handling

After first use, the product may be stored at or below 25 °C for up to 28 days and must be discarded if not used.

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

1.5.1.2 Labelling

A. PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER PACKAGING OF VIALS

1. Name of the Medicinal Product:

Recombinant Human Follicle Stimulating Hormone (follitropin alfa) 1200 IU/1.92 mL solution for injection in multiple use vial.

2. Statement of Active Substance(s):

Each vial delivers 1200 IU follitropin alfa, equivalent to 88 micrograms, per 1.92 mL.

3. List of Excipients:

- Monosodium dihydrogen phosphate monohydrate
- Di sodium hydrogen phosphate dihydrate
- Sodium Chloride
- Polysorbate 20
- Ortho phosphoric acid**
- Sodium hydroxide**