MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Not applicable as rHu FSH is a parentral product, presented in a vial.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

1. Name of the medicinal product and route(s) of administration:

Product Name:

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

Route of administration: Subcutaneous (s.c.)

2. 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.

3. Expiry Date: Two years from the date of manufacturing

4. Batch Number: As per the actual

5. Strengths and Presentations.

Each vial contains 1200 IU of rHu FSH per 1.92 mL.

1.4.1.3 PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even

- If their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet,
- Please tell your doctor or pharmacist.

In this leaflet:

1. What rHu FSH is and what it is used for?

What rHu FSH is

rHu FSH contains a medicine called "follitropin alfa". Follitropin alfa is a type of "Follicle Stimulating Hormone" (FSH) which belongs to the family of hormones called "gonadotropins". Gonadotropins are involved in reproduction and fertility.

rHu FSH of Intas Pharmaceuticals is identical to, the active ingredient of GONAL-f® (Merck Serono Inc) in structure and function.

What is rHu FSH used for

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.

2. Before you take rHu FSH

Contraindications

rHu FSH (Follitropin α) is contraindicated in women 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.

Do not use rHu FSH:

- If you are allergic (hypersensitive) to Follicle Stimulating Hormone or any of the other ingredients of follitropin alfa listed in section 6.
- If you have a tumour in your hypothalamus or pituitary gland (both are parts of the brain).

  If you are a woman:

  - With large ovaries or sacs of fluids within the ovaries (ovarian cysts) of unknown origin.
  - With unexplained vaginal bleeding.
  - With cancer in your ovaries, womb or breasts.
  - With a condition that usually makes normal pregnancy impossible, such as ovarian failure (early menopause), or malformed reproductive organs.

  If you are a man:

  - With damaged testicles that cannot be healed.

Take special care with rHu FSH

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.

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.

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.

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.

3. How to use Follitropin alfa (r-Hu FSH)

Always use follitropin alfa exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Using this medicine

- Follitropin alfa is intended to be given by injection just under the skin (subcutaneously).
- The first injection of follitropin alfa should be given under supervision of your doctor.

- Your doctor or nurse will show you how to inject follitropin alfa before you can inject yourself.
- If you administer follitropin alfa to yourself, please carefully read and follow the instructions provided in package insert.

How much to use

Your doctor will decide how much medicine you will take and how often. The doses described below are stated in International Units (IU) and millilitres (mL).

Women

If you are not ovulating and have irregular or no periods.

- Follitropin alfa is usually given every day.
- If you have irregular periods, start using follitropin alfa within the first 7 days of your menstrual cycle. If you do not have periods you can start using the medicine on any convenient day.
- The usual starting dose of follitropin alfa is 75 to 150 IU (0.12 to 0.24 mL) each day.
- Your dose of follitropin alfa may be increased every 7 or every 14 days by 37.5 to 75 IU, until you get the desired response.
- The maximum daily dose of follitropin alfa is usually not higher than 225 IU (0.36 mL).
- When you get the desired response, you will be given a single injection of 250 micrograms of "recombinant hCG" (r-hCG, an hCG made in a laboratory by a special DNA technique), or 5,000 to 10,000 IU of hCG, 24 to 48 hours after your last follitropin alfa injection. The best time to have sex is on the day of the hCG injection and the day after.

If your doctor cannot see a desired response after 4 weeks, that treatment cycle with follitropin alfa should be stopped. For the following treatment cycle, your doctor will give you a higher starting dose of follitropin alfa than before. If your body responds too strongly, your treatment will be stopped and you will not be given any hCG (see section 2, OHSS). For the following cycle, your doctor will give you a lower dose of follitropin alfa than before.

If you are not ovulating, having no periods and have been diagnosed with very low levels of FSH and LH hormones

- The usual starting dose of follitropin alfa is 75 to 150 IU (0.12 to 0.24 mL) together with 75 IU (0.12 mL) of lutropin alfa.
- You will use these two medicines each day for up to five weeks.
- Your dose of follitropin alfa may be increased every 7 or every 14 days by 37.5 to 75 IU, until you get the desired response.
- When you get the desired response, you will be given a single injection of 250 micrograms of "recombinant hCG" (r-hCG, an hCG made in a laboratory by a special DNA technique), or 5,000 to 10,000 IU of hCG, 24 to 48 hours after your last injections of follitropin alfa and lutropin alfa. The best time to have

sex is on the day of the hCG injection and the day after. Alternatively, intrauterine insemination may be performed by placing the sperm into the womb cavity.

If your doctor cannot see a response after 5 weeks, that treatment cycle with follitropin alfa should be stopped. For the following cycle, your doctor will give you a higher starting dose of follitropin alfa than before. If your body responds too strongly, your treatment with follitropin alfa will be stopped and you will not be given any hCG (see section 2, OHSS). For the following cycle, your doctor will give you a lower dose of follitropin alfa than before.

If you need to develop several eggs for collection prior to any assisted reproductive technology

- The usual starting dose of follitropin alfa is 150 to 225 IU (0.24 to 0.36 mL) each day, from day 2 or 3 of your treatment cycle.
- Follitropin alfa dose may be increased, depending on your response. The maximum daily dose is 450 IU (0.72 mL).
- Treatment is continued until your eggs have developed to a desired point. This usually takes about 10 days but can take any time between 5 and 20 days. Your doctor will use blood tests and/or an ultrasound machine to check when this is.
- When your eggs are ready, you will be given a single injection of 250 micrograms "recombinant hCG" (r-hCG, an hCG made in a laboratory by a special recombinant DNA technique), or 5,000 IU to 10,000 IU of hCG, 24 to 48 hours after the last follitropin alfa injection. This gets your eggs ready for collection.

In other cases, your doctor may first stop you from ovulating by using a gonadotropin-releasing hormone (GnRH) agonist or antagonist. Then follitropin alfa is started approximately two weeks after start of agonist treatment. The follitropin alfa and GnRH agonist are then both given until your follicles develop as desired. For example, after two weeks of GnRH agonist treatment, 150 to 225 IU follitropin alfa is administered for 7 days. The dose is then adjusted according to your ovarian response. When GnRH antagonist is used, it is administered from the 5th or 6th day of follitropin alfa treatment and continued until ovulation induction.

Men

- The usual dose of follitropin alfa is 150 IU (0.24 mL) together with hCG.
- You will use these two medicines three times a week for at least 4 months.
- If you have not responded to treatment after 4 months, your doctor may suggest that you continue using these two medicines for at least 18 months.

If you use more follitropin alfa than you should

The effects of taking too much follitropin alfa are unknown, nevertheless one could expect Ovarian Hyper-Stimulation Syndrome (OHSS) to occur, which is described in section 4. However the OHSS will only occur if hCG is also administered (see section 2, OHSS).

If you forget to use follitropin alfa

If you forget to use follitropin alfa, do not take a double dose to make up for a forgotten dose. Please talk to your doctor as soon as you notice that you forgot a dose. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side 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

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. How to Store

Store in a refrigerator (2°C - 8°C) and protect from light. Do not freeze. Keep out of the reach and sight of children.

6. Further information

What follitropin alfa contains

The active substance is follitropin alfa.

There are 625 IU (equivalent to 45.8 micrograms) of follitropin alfa in each mL of solution.

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

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

The other ingredients are Monosodium dihydrogen phosphate monohydrate, Di sodium hydrogen phosphate dihydrate, Sodium Chloride, Polysorbate 20, Ortho-phosphoric acid, Sodium hydroxide, Mannitol, Trehalose dihydrate, L-Methionine, Phenol and Water for injection.

What follitropin alfa looks like and contents of the pack

Follitropin alfa is presented as a clear, colourless solution for injection in multi-dose vial.

Marketing Authorisation Holder

Not Applicable