SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal product:

1.1 Product name

Recombinant Human Follicle Stimulating Hormone Injection IH

1.2 Strength

450 IU (33.0 µg) / 900 IU (66.0 µg).

1.3 Pharmaceutical dosage form

Solution for Injection in Prefilled Pen

2. Qualitative and Quantitative compositions

Each Prefilled pen containing one cartridge contains:

• Recombinant Human Follicle Stimulating Hormone Injection IH (66.0 µg) /1.5ml Solution for injection in Prefilled Pen.

• Recombinant Human Follicle Stimulating Hormone Injection IH (33.0 µg) /0.75ml Solution for injection in Prefilled Pen.

• Excipients: Disodium Hydrogen Phosphate Anhydrous B.P., Mannitol B.P., Sucrose B.P., L-Methionine B.P., Tween 20 B.P., Meta-cresol B.P, Water for injection USP..

3. Pharmaceutical form:

- Foligraf 900 IU (66.0 µg) /1.5 ml Solution for Injection in Prefilled Pen

  One cartridge contains a net total dose of 900 IU (66.0 µg) Follicle-stimulating Hormone (Human Recombinant) in 1.5 ml aqueous solution. The solution for injection contains the active substance produced by genetic engineering of a Chinese hamster ovary (CHO) cell line.

- Foligraf 450 IU (33.0 µg) /0.75 ml Solution for Injection in Prefilled Pen

  One cartridge contains a net total dose of 450 IU (33.0 µg) Follicle-stimulating Hormone (Human Recombinant) in 0.75 ml aqueous solution.

The solution for injection contains the active substance produced by genetic Chinese hamster ovary (CHO) cell line.

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.
- 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.
- rFSH in association with a luteinising hormone (LH) preparation is recommended for the stimulation of follicular development in women with severe LH and FSH deficiency. In clinical trials these patients were defined by an endogenous serum LH level < 1.2 IU/L.
- **In adult men**
- rFSH is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism with concomitant human Chorionic Gonadotropin (hCG) therapy.

4.2 Posology and method of administration

Treatment with Foligraf 450 IU (33.0 µg) /900 IU (66.0 µg) Solution for Injection in Prefilled Pen should be initiated under the supervision of a physician experienced in the treatment of fertility problems. Foligraf 450 IU (33.0 µg) /900 IU (66.0 µg) Solution for Injection in prefilled pen is intended for subcutaneous administration. The dosage recommendations given for 450 IU (33.0 µg) /900 IU (66.0 µg) Solution for injection in prefilled pen are those in use for urinary FSH.

Clinical assessment of indicates that its daily doses, regimens of administration, and treatment monitoring procedures should not be different from those currently used for urinary FSH-containing preparations. However, the study reports conclude that, Foligraf is more effective than urinary FSH

in terms of a lower total dose and a shorter treatment period needed to achieve pre-ovulatory conditions. It is advised to adhere to the recommended starting doses indicated below.

1. Women with anovulation (including PCOD):

The object of 450 IU (33.0 µg) /900 IU (66.0 µg) cartridge in Prefilled multidose Pen therapy is to develop a single mature Graafian follicle from which the ovum will be liberated after the administration of HCG. Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen may be given as a course of daily injections.

In menstruating patients' treatment should commence within the first 7 days of the menstrual cycle. Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and/or oestrogen secretion. A commonly used regimen commences at 75 - 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. The maximal daily dose is usually not higher than 225 IU of FSH. If a patient fails to respond adequately after 4 weeks of treatment, that cycle should be abandoned, and the patient should recommence treatment at a higher starting dose than in the abandoned cycle. When an optimal response is obtained, a single injection of 5 000 IU., up to 10 000 IU. HCG should be administered 24 - 48 hours after the last Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for Injection in prefilled pen. 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 (please see warnings). Treatment should recommence in the next cycle at a dosage lower than that of the previous cycle.

2. Women undergoing ovarian stimulation for multiple follicular development prior to in vitro fertilisation or other assisted reproductive technologies

A commonly used regimen for superovulation involves the administration of 150-225 IU of Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen 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 oestrogen 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 (6500 IU) r-hCG or 5,000 IU up to 10,000 IU hCG is administered 24-48 hours after the last Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen 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, Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen 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, 150-225 IU Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen 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.

3. Women with anovulation resulting from severe LH and FSH deficiency

In LH and FSH deficient women (hypogonadotrophic hypogonadism), the objective of Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen therapy in association with lutropin alfa is to develop a single mature Graafian follicle from which the oocyte will be liberated after the administration of human chorionic gonadotropin (hCG). Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen should be given as a course of daily injections simultaneously with lutropin alfa. Since these patients are amenorrhoeic and have low endogenous oestrogen secretion, treatment can commence at any time.

A recommended regimen commences at 75 IU of recombinant LH (rLH) daily with 75-150 IU FSH. Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and oestrogen response.

If an FSH dose increase is deemed appropriate, dose adaptation should preferably be after 7-14 day intervals and preferably by 37.5-75 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 24-48 hours after the last Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen and rLH injections. The patient is recommended to have coitus on the day of, and on the day following, hCG administration. Alternatively, IUI may be performed.

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.

4. Men with hypogonadotrophic hypogonadism

Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen 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.

5. Special populations

Elderly

There is no relevant use of Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen in the elderly population. Safety and effectiveness of Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen in elderly patients have not been established.

Renal or hepatic impairment

Safety, efficacy and pharmacokinetics of Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen in patients with renal or hepatic impairment have not been established.

Pediatric population

There is no relevant use of Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen in the pediatric population.

4.3 Contra-indications

Foligraf must not be used in:

- Hypersensitivity to Foligraf, FSH or to any of the excipients
- Case of tumors of the hypothalamus and pituitary gland
- Ovarian enlargement or cyst not due to polycystic ovarian disease
- Gynecological hemorrhages of unknown aetiology
- Ovarian, uterine or mammary carcinoma.

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Foligraf should not be used when an effective response cannot be obtained in conditions, such as:

- Primary ovarian failure
- Malformations of sexual organs incompatible with pregnancy
- Fibroid tumors of the uterus incompatible with pregnancy

4.4 Special warning and precautions for use

Recombinant Human Follicle Stimulating Hormone for Injection 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.

Gonadotrophin therapy requires a certain time commitment by physicians and supportive health professionals, as well as the availability of appropriate monitoring facilities. In women, safe and effective use of Foligraf calls for monitoring of ovarian response 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.

The lowest effective dose in relation to the treatment objective should be used. Self-administration of Foligraf should only be performed by patients who are well motivated, adequately trained and with access to expert advice. The first injection of Foligraf should be performed under direct medical supervision. 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 hypothalamic tumors, and appropriate specific treatment given. Patients undergoing stimulation of follicular growth, whether in the frame of a treatment for anovulatory infertility or ART procedures, may experience ovarian enlargement or develop hyper stimulation. Adherence to recommended 'Foligraf dosage and regimen of administration, and careful monitoring of therapy will minimize the incidence of such events. Acute interpretation of the indices of follicle development and maturation require a physician who is experienced in the interpretation of the relevant tests. If an FSH dose increase is deemed appropriate, dose adaptation should preferably be at 7 to 14-day intervals and preferably with 37.5-75 IU increments.

Ovarian Hyperstimulation Syndrome (OHSS):

OHSS is a medical event distinct from uncomplicated ovarian enlargement. OHSS is a syndrome 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, acute pulmonary distress, and thromboembolic events. Excessive ovarian response to gonadotrophin treatment seldom gives

rise to OHSS unless HCG is administered to trigger ovulation. Therefore, in cases of ovarian hyperstimulation it is prudent to withhold HCG and advise the patient to refrain from coitus or to use barrier methods for at least 4 days. OHSS may progress rapidly (within 24 hours to several days) to become a serious medical event, therefore patients should be followed for at least two weeks after HCG administration.

To minimize the risk of OHSS or of multiple pregnancy, ultrasound scans as well as oestradiol measurements are recommended. In anovulation the risk of OHSS and multiple pregnancy is increased by a serum oestradiol > 900 pg/mL (3300 pmol/l) and more than 3 follicles of 14 mm or more in diameter. In ART there is an increased risk of OHSS with a serum oestradiol > 3000 pg/mL (11000 pmol/l) and 20 or more follicles of 12 mm or more in diameter. When the oestradiol level is > 5500 pg/mL (20200 pmol/l) and where there are 40 or more follicles in total, it may be necessary to withhold HCG administration. Adherence to recommended 'Foligraf dosage, regimen of administration and careful monitoring of therapy will minimize the incidence of ovarian hyper stimulation and multiple pregnancy. In ART, aspiration of all follicles prior to ovulation may reduce the occurrence of hyper stimulation. OHSS may be more severe and more protracted if pregnancy occurs. Most often, OHSS occurs after hormonal treatment has been discontinued and reaches its maximum at about seven to ten days following treatment. Usually, OHSS Resolves spontaneously with the onset of menses. If severe OHSS occurs, gonadotrophin treatment should be stopped if still ongoing, the patient hospitalized and specific therapy for OHSS started. This syndrome occurs with higher incidence in patients with polycystic ovarian disease.

Multiple pregnancies:

Multiple pregnancies, especially high order, carries an increase risk in adverse maternal and perinatal outcomes. In patients undergoing ovulation induction with 'Foligraf, the incidence of multiple pregnancies is increased as compared with natural conception. The majority of multiple conceptions are twins. To minimize the risk of multiple pregnancies, 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 wastage:

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

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 drug regimens for infertility treatment. It is not yet established whether or not treatment with gonadotrophins increases the baseline risk of these tumors 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 generally recognized risk factors for thrombo-embolic events, such as personal or family history, treatment with gonadotrophins may further increase the risk. In these women, the benefits of gonadotrophin administration need to be weighed against the risks. It should be noted however, that pregnancy itself also carries an increased risk of thromboembolism.

Treatment in men

Elevated endogenous FSH levels are indicative of primary testicular failure. Such patients are unresponsive to r FSH/hCG therapy. Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen 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 drugs, other forms of interactions

Concomitant use of Follicle Stimulating hormone Injection (Human Recombinant) (r-hFSH) with other agents used to stimulate ovulation (e.g. HCG, clomiphene citrate) may potentiate the follicular response, whereas concurrent use of a GnRH agonist to induce pituitary desensitization may increase the dosage of Follicle Stimulating hormone Injection (Human Recombinant) (r-hFSH) 'needed to elicit an adequate ovarian response. No other clinically significant drug interaction has been reported during Follicle Stimulating hormone Injection (Human Recombinant) (r-hFSH)

4.6 Use in pregnancy and lactation

Use during pregnancy: There is no indication for use of Follicle Stimulating hormone Injection (Human Recombinant) (r-hFSH) during pregnancy. No teratogenic risk has been reported, following controlled ovarian hyperstimulation, in clinical use with gonadotrophins. In case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of recombinant human follicular stimulating hormone. However, to date, no particular malformative effect has been reported. No teratogenic effect has been observed in animal studies.

Use during lactation:

Follicle Stimulating hormone Injection (Human Recombinant) (r-hFSH) is not indicated during lactation. During lactation, the secretion of prolactin can entail a poor prognosis to ovarian stimulation.

4.7 Effects on ability to drive and operate machine

No studies on the effects on ability to drive and use machines have been performed.

4.8 Undesirable effects

Treatment in women:

Very Common (> 1/10)

- Ovarian cysts;
- Mild to severe injection site reaction (pain, redness, bruising, swelling and/or irritation at the site of injection);
- Headache.

Common (≥ 1/100 to < 1/10):

- Mild to moderate OHSS;
- Abdominal pain and gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal cramps and bloating.
- Gynaecomastia, varicocele

Uncommon (≥ 1/1,000 to < 1/100):

- Severe OHSS.

Rare (≥ 1/10, 000 to < 1/1,000):

- Ovarian torsion, a complication of OHSS.

Very rare (< 1/10 000):

- Thromboembolism usually associated with severe OHSS;
- Mild systemic allergic reactions (erythema, rash or facial swelling).
- Exacerbation or aggravation of asthma

4.9 Overdoses

The effects of an overdose of r-hFSH are unknown, nevertheless one could expect ovarian hyperstimulation syndrome to occur, which is further described in Special Warnings and Special Precautions for Use.

5. Pharmacological properties :

5.1 Mechanism of Action

FSH is indispensable in normal follicular growth and maturation, and gonadal steroid production. In the female the level of FSH is critical for the onset and duration of follicular development, and consequently for the timing and number of follicles reaching maturity. Follicle Stimulating hormone Injection (Human Recombinant) (r-hFSH) can thus be used to stimulate follicular development and steroid production in selected cases of disturbed gonadal function.

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: gonadotrophins.

'Foligraf Solution for injection in prefilled multidose pen is a preparation of follicle stimulating hormone produced by genetically engineered Chinese Hamster Ovary (CHO) cells. In women, the most important effect resulting from parenteral administration of FSH is the development of mature Graafian follicles.

5.3 Pharmacokinetic properties

Following subcutaneous administration, Follicle Stimulating hormone Injection (Human Recombinant) (r-hFSH) is distributed to the extra cellular fluid space with an initial half-life of around 2 hours and eliminated from the body with a terminal half-life of about one day. The steady state volume of distribution and total clearance are 10 L and 0.6 L/h, respectively. One eighth of the Recombinant Human Stimulating hormone dose is excreted in the urine. Following subcutaneous administration, the absolute bioavailability is about 70%. Following repeated administration, Recombinant Human Stimulating Hormone accumulates 3-fold achieving a steady state within 3-4 days.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

In an extensive range of animal toxicity studies studied in laboratory animal models (mice, rats, rabbits), no significant findings were observed.

7. Pharmaceutical particulars :

7.1 List of excipients:

Disodium hydrogen phosphate anhydrous	BP
Mannitol	BP
Sucrose	BP
L-Methionine	BP
Tween 20 (Polysorbate 20)	BP
meta-Cresol	BP
Sodium hydroxide	BP
Phosphoric acid	BP
WFI	USP

7.2 Incompatibilities:

This medicinal product must not be mixed with other medicinal products except those mentioned.

7.3 Shelf-life:

24 months from the date of manufacturing.

7.4 Special precaution for storage:

Keep out of reach of children.

Store between 2°C - 8°C. Do not freeze. Protect from light.

Store in the original package.

Foligraf 450 IU (33.0 µg) / 900 IU (66.0 µg) Solution for injection in prefilled pen should be used within 28 days after first dose, if the drug is stored below 25°C.

8. Nature and contents of container:

8.1.1 Foligraf 900 IU (66.0 µg) / 1.5ml Solution for Injection in Prefilled Pen

Each Carton contains:

1 Foligraf multi-dose prefilled pen

14 sterile Pen needles

8.1.2 Foligraf 450 IU (33.0 µg) / 0.75 ml Solution for Injection in Prefilled Pen

Each Carton contains:

1 Foligraf multi-dose prefilled pen

7 sterile Pen needles

9. Marketing Authorization Holder :

Bharat Serums and Vaccines Limited,

Plot No: K-27, K-27 Part and K-27/1, Anand Nagar, Jambivili Village,

Additional MIDC, Ambernath (E) - 421506,

Thane, Maharashtra, India

10. Marketing Authorization Number :

Not Applicable

11. Date of First Authorization / Renewal of Authorization :

Not Applicable

12. Date of revision of the text :

Not Applicable