Chinese Hamster Ovary (CHO) cells.

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

Steroidogenesis, despite un-measurable LH levels.

Achieving a steady state within 3-4 days. In women whose endogenous gonadotrophin secretion is suppressed, bioavailability is about 70%. Following repeated administration, 3-fold accumulates.

LH measurement performed in different laboratories.

LH level <1.2 IU/l as measured in laboratory. However, it should be taken into account that there are variations between LH measurements performed in different laboratories.

Steady state volume of distribution and total clearance are 10 l and 0.6 l/h, respectively. One eighth of the dose is excreted in the urine. Following subcutaneous administration, the absolute bioavailability is about 70%.

Following intravenous administration, 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 FOLIGRAF™ (r-hFSH) dose is excreted in the urine. Following subcutaneous administration, the absolute bioavailability is about 70%.

Following repeated administration, FOLIGRAF™ (r-hFSH) accumulates 3-fold achieving a steady state within 3-4 days. In women whose endogenous gonadotrophin secretion is suppressed, FOLIGRAF™ (r-hFSH) has nevertheless been shown to effectively stimulate follicular development and steroidogenesis, despite un-measurable LH levels.

Preclinical safety data:

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

Incompatibilities:

This medicinal product must not be mixed with other medicinal products except those mentioned. The reconstituted solution should not be administered if it contains particles or it is not clear.

Special precautions for storage:

Keep out of reach of children.

Keep between 2°C - 8°C.

Do not freeze. Protect from light.

Presentation:

Each vial contains:

Recombinant-Human Follicle Stimulating Hormone .............................................................. 75 I.U. / 150 I.U.

For immediate and single use following first opening and reconstitution.

For Subcutaneous use only

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Manufactured in India by

For Subcutaneous use only

Bharat Serums and Vaccines Limited

Clinically, it was observed that, FOLIGRAF™ (r-hFSH) therapy is to develop a single mature Graafian follicle from which the ovum will be liberated after the administration of HCG. FOLIGRAF™ (r-hFSH) may be given as a course of daily injections. Following repeated administration, the absolute bioavailability is about 70%.

Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by transvaginal and/or oestrogen secretion. It is recommended to commence at 75-150 IU FSH daily and is increased preferably by 37.5 or 75 IU at 7 or preferably 14 days intervals if necessary, to obtain an adequate, but not excessive, response. 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 commence treatment at a higher starting dose than in the abandoned cycle. When an optimal response is obtained, a single injection of 5000 IU, up to 10 000 IU HCG should be administered 24 - 48 hours after the last FOLIGRAF™ (r-hFSH) injection. The patient is recommended to have cuffus 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 (see warnings).

Treatment should recommence in the next cycle at a dosage lower than that of the previous cycle.

1. Women with anovulation (including PCD): The object of FOLIGRAF™ (r-hFSH) therapy is to develop a single mature Graafian follicle from which the ovum will be liberated after the administration of HCG. FOLIGRAF™ (r-hFSH) 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 transvaginal and/or oestrogen secretion. It is recommended to commence at 75-150 IU FSH daily and is increased preferably by 37.5 or 75 IU at 7 or preferably 14 days intervals if necessary, to obtain an adequate, but not excessive, response. 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 commence treatment at a higher starting dose than in the abandoned cycle. When an optimal response is obtained, a single injection of 5000 IU, up to 10 000 IU HCG should be administered 24 - 48 hours after the last FOLIGRAF™ (r-hFSH) injection. The patient is recommended to have cuffus 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 (see warnings).

2. Women undergoing ovarian stimulation for multiple follicular developments prior to in vitro fertilization or other assisted reproductive techniques: A commonly used regimen for superovulation involves the administration of 150-225 IU of r-hFSH 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 ultrasonic 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 up to 10 000 IU HCG is administered 24-48 hours after the last FOLIGRAF™ (r-hFSH) injection to induce final follicular maturation. Down-regulation with a gonadotropin-releasing hormone (GnRH) agonist is now commonly used in order to suppress the endogenous LH surge and to control tonic FSH levels and LH fluctuations. In a commonly used protocol, FOLIGRAF™ (r-hFSH) 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™ (r-hFSH) 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.

**Contraindications:**
- Hypersensitivity to FOLIGRAF™ (r-hFSH), FSH or to any of the excipients
- Pregnancy
- History of ovarian hyperstimulation syndrome
- History of idiopathic thrombocytopenic purpura
- History of tumors of the uterus incompatible with pregnancy
- History of tumors of the breast incompatible with pregnancy
- History of tumors of the ovaries incompatible with pregnancy
- History of tumors of the hypothalamus and pituitary gland
- History of tumors of the smoked incompatible with pregnancy
- History of ovarian hyperstimulation syndrome (OHSS)
- History of uterine or uterine carcinoma

FOLIGRAF™ (r-hFSH) should not be used when an effective response cannot be obtained, such as:
- Primary ovarian insufficiency
- Malformations of sexual organs incompatible with pregnancy
- History of prior idiopathic thrombocytopenic purpura
- History of severe OHSS

**Special warnings and special precautions for use:**

**FOLIGRAF™ (r-hFSH):**
- It is a potent gonadotrophic substance capable of causing mild to severe adverse reactions
- It should be observed by physicians who are thoroughly familiar with infertility problems and their management
- Gonadotropin 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™ (r-hFSH) calls for monitoring 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 in some patients. The lowest effective dose in relation to the treatment objective should be used. Self-administration of FOLIGRAF™ (r-hFSH) should only be performed by patients who are well motivated, adequately trained and with expert advice. The first injection of FOLIGRAF™ (r-hFSH) should be performed under 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, anemia or other deficiencies, 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™ (r-hFSH) 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 comparison of FOLIGRAF™ (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 FOLIGRAF™ (r-hFSH) needed to elicit an adequate ovarian response. No other clinically significant drug interaction has been reported during FOLIGRAF™ (r-hFSH) therapy.

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, dyspnea, oliguria, caviglia and gastrointestinal symptoms including nausea, vomiting and diarrhea. Clinical evaluation may reveal hypovolaemia, haemococoncentration, thrombocytopenia, pleural effusion, ascites, hepatic dysfunction, renal failure, hyponatraemia, hyperkalaemia, and, in some cases, thromboembolic events. Excessive ovarian enlargement in the presence of significantly elevated serum estradiol levels and serum progesterone levels may contribute to OHSS. OHSS usually occurs 2–5 days after HCG administration. 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 24 hours to several days to become a serious medical event, therefore patients should be followed for at least 2 weeks after HCG administration. To minimize the risk of OHSS or of multiple pregnancy, ultrasound scans as well as oestradiol measurements are recommended. In anovulatory cycles the inflection of HCG 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 increased risk in adverse maternal and perinatal outcomes. In patients undergoing ovulation induction with FOLIGRAF™ (r-hFSH), 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.

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 in the normal 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 thromboembolic 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 thrombosis.

Interaction with other medicinal products and other forms of interaction:

Concomitant use of FOLIGRAF™ (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 FOLIGRAF™ (r-hFSH) needed to elicit an adequate ovarian response. No other clinically significant drug interaction has been reported during FOLIGRAF™ (r-hFSH) therapy.

Pregnancy and lactation:

- Use during pregnancy:
  - There is no indication for use of FOLIGRAF™ (r-hFSH) during pregnancy. No teratogenic risk has been reported. Following controlled ovarian hyper stimulation, in clinical use with gonadotrophins, in case of exposure during pregnancy, clinical trials do not suffice to exclude a teratogenic effect of recombinant FOLIGRAF™ (r-hFSH). However, to date, no particular malformative effects have been reported. No teratogenic effect has been observed in animal studies.

- Use during lactation:
  - FOLIGRAF™ (r-hFSH) is not indicated during lactation. During lactation, the secretion of prolactin can entail a poor prognosis to ovarian stimulation.

Effects on ability to drive and use machines:

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

**UNDESIRABLE EFFECTS**

- Treatment in women: Very Common (> 1/10)
- Discontinuation: Severe
- Headache.

- Use in the elderly: Premenopausal women: Risk increased with age.
- Pregnancy: There is no indication for use of FOLIGRAF™ (r-hFSH) during pregnancy. No teratogenic risk has been reported. Following controlled ovarian hyper stimulation, in clinical use with gonadotrophins, in case of exposure during pregnancy, clinical trials do not suffice to exclude a teratogenic effect of recombinant FOLIGRAF™ (r-hFSH). However, to date, no particular malformative effects have been reported. No teratogenic effect has been observed in animal studies.

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