

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

Recombinant-Human Follicle Stimulating Hormone for Injection (r-hFSH)

FOLIGRAF™

75 I.U. / 150 I.U.

Freeze Dried

For Subcutaneous use only

COMPOSITION :

Each vial contains :

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

Excipients :

Sucrose I.P., Di-sodium Hydrogen Phosphate I.P., Mannitol I.P., Tween 20 I.P. and Methionine (IH).

CLINICAL PARTICULARS :

Therapeutic indications :

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

≥ Stimulation of multifollicular development in patients undergoing superovulation for assisted reproductive technologies (ART) such as in vitro fertilization (IVF), gamete intra-fallopian transfer (GIFT) and zygote intra-fallopian transfer (ZIFT).

Posology and method of administration :

Treatment with **FOLIGRAF™** (r-hFSH) should be initiated under the supervision of a physician experienced in the treatment of fertility problems. **FOLIGRAF™** (r-hFSH) is intended for subcutaneous administration. The powder should be reconstituted immediately prior to use with the solvent provided. In order to avoid the injection of large volumes, up to 3 vials of product may be dissolved in 0.5ml of solvent. The dosage recommendations given for **FOLIGRAF™** (r-hFSH) are those in use for urinary FSH. Clinical assessment of **FOLIGRAF™** (r-hFSH) 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™** (r-hFSH) 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 **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 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 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™** (r-hFSH) 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 (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 developments prior to in vitro fertilization or other assisted reproductive technologies :

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 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 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 gonadotrophin-releasing hormone (GnRH) agonist 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™** (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 :

FOLIGRAF™ (r-hFSH) must not be used in :

- ≥ hypersensitivity to **FOLIGRAF™** (r-hFSH), 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
- ≥ gynaecological haemorrhages of unknown aetiology
- ≥ ovarian, uterine or mammary carcinoma

FOLIGRAF™ (r-hFSH) should not be used when an effective response cannot be obtained, such as :

- ≥ primary ovarian failure
- ≥ malformations of sexual organs incompatible with pregnancy
- ≥ fibroid tumors of the uterus incompatible with pregnancy

Special warnings and special precautions for use :

FOLIGRAF™ (r-hFSH) 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™** (r-hFSH) 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™** (r-hFSH) should only be performed by patients who are well motivated, adequately trained and with access to expert advice. The first injection of **FOLIGRAF™** (r-hFSH) 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™** (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 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 - 14 day intervals and preferably with 37.5-75 IU increments.

No direct comparison of r-hFSH/LH versus human menopausal gonadotrophin (HMG) has been performed. Comparison with historical data suggests that the ovulation rate obtained with **FOLIGRAF™** (r-hFSH)/LH is similar to what can be obtained with HMG.

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™** (r-hFSH) 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™** (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.

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 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 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 thrombo-embolic events.

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 data are not sufficient to exclude a teratogenic effect of recombinant **FOLIGRAF™** (r-hFSH). However, to date, no particular malformative effect has 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)

≥ Ovarian cysts;

≥ Mild to severe injection site reaction (pain, redness, bruising, swelling and/or irritation at the site of injection);

≥ Headache.

Common (1/100 1/10) :

≥ Mild to moderate OHSS

≥ Abdominal pain and gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal cramps and bloating.

Uncommon (1/1000 1/100) :

≥ Severe OHSS

Rare (1/10 000 1/1000) :

≥ 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).

Overdose :

The effects of an overdose of **FOLIGRAF™** (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.

PHARMACOLOGICAL PROPERTIES :**Pharmacodynamic properties :**

Pharmacotherapeutic group: gonadotrophins.

FOLIGRAF™ (r-hFSH) 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. Patients with severe FSH and LH deficiency were defined by an endogenous serum 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.

Pharmacokinetic properties :

Following intravenous administration, **FOLIGRAF™** (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 **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.

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

Store in the original package.

For immediate and single use following first opening and reconstitution.

Presentation :

The product is supplied in vial containing sterile, freeze dried white to off white powder having Recombinant-Human Follicle Stimulating Hormone activity of 75 I.U. / 150 I.U.

Each vial is accompanied by an ampoule containing 0.5ml of Sterile Water for Injection I.P.

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Manufactured in India by :

BHARAT SERUMS AND VACCINES LIMITED

Plot No. K-27, Additional M.I.D.C., Ambernath (E) - 421 501.