SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the product:

1.1 Product name:

FOLIGRAF 75 IU
Recombinant - Human Follicle Stimulating Hormone for Injection – Freeze dried

1.2 Strength

75 I.U.

1.3 Pharmaceutical dosage form:

Freeze dried powder for injection

2. Qualitative and Quantitative composition:

Name of component
Recombinant human follicle stimulating hormone
Disodium hydrogen phosphate anhydrous
Mannitol
Sucrose
Methionine
Tween 20 (Polysorbate 20)

3. Pharmaceutical form:

Freeze dried powder for Injection.

4. Clinical particulars:

4.1 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).

4.2 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 byultrasound 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.

4.3 Contra-indications:

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.

4.4 Special warning and 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.

4.5 Interaction with other medicinal products and other forms of interactions

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.

4.6 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.

4.7 Effects on ability to drive and use 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 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).

4.9 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.

5. 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.

6. Pharmaceutical particulars :

6.1 List of Excipients:

1. Disodium Hydrogen Phosphate Anhydrous BP
2. Mannitol BP
3. Sucrose BP
4. Methionine BP
5. Tween 20 (Polysornbate 20) BP

6.2 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.

6.3 Shelf life:

24 months.

6.4 Special precautions for storage:

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

6.5 Nature and contents of container:

The lyophilized powder is filled in USP type – I, 2 ml glass vial, further packed in a carton along with a pack insert.

7. Marketing authorization holder:

M/s. Bharat Serums & Vaccines Ltd.
17 th Floor, Hoechst House. Nariman Point.
Mumbai -400 610. India.

8. Marketing authorization number

06477/07894/REN/2021

9. Date of first authorization / renewal of authorization

Aug 12, 2021

10. Date of revision of the text

Not Applicable.