# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Foliculin 150 HP (Urofollitropin for Injection B.P. 150 IU) (Highly Purified) (Freeze Dried)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains :

Urofollitropin B.P. ..... 150 I.U.

Qualitative and quantitative composition of Foliculin -150 HP

| Ingredient | Specification | Quantity/Vial | Justification for the use of ingredient |
|---|---|---|---|
| Urofolitropin(HP) | BP | 150 IU | API |
| Mannitol | BP | 30 mg | Bulking agent |
| Sucrose | BP | 10 mg | Protein Stabilizer |
| Anhydrous Disodium Hydrogen phosphate | BP | 1.42 mg | pH mainrenenance |
| Sodium Ascorbate | BP | 0.1 mg | Antioxidant |
| Phosphoric Acid* | BP | q. s. | pH adjustment |
| Sodium Hydroxide* | BP | q. s. | pH adjustment |
| Water for Injection | USP | q.s. | Solvent |

* For pH adjustment

B.P.: British Pharmacopoeia

## 3. PHARMACEUTICAL FORM:

**Dosage form:** Injection (Freeze Dried Powder for Injection)

**Description: Foliculin 150 HP** is an almost white or slightly yellow powder or cake.

## 4. CLINICAL CHARACTERISTICS

### 4.1 Therapeutic Indications:

FOLICULIN HP and HuCOG HP given in a sequential manner are indicated for introduction of ovulation on patient with Polycystic Ovarian Disease (PCOD) who have an elevated LH/FSH ration and who have failed to respond to adequate clomiphene citrate therapy.

FOLICULIN HP and HCG may also be used to stimulate the development of multiple oocytes in ovulatory patient participating in an in vivo fertility program.

### 4.2 Posology and Method of Administration

**Posology:**

The dose of FOLICULIN HP to produce maturation of follicle must be individualized for each patient.it is recommended that initial dose to any patient should be 75 I.U. of FOLICULIN HP per day administered subcutaneous for 7 – 12 days followed by HCG 5000 I.U.to 10000 I.U.one day after last dose of FOLICULIN HP. Administration of FOLICULIN HP may exceed 12 days if inadequate follicle development is indicated by oestrogen and/or ultrasound measurements.

If there is evidence of ovulation but no pregnancy, repeat above dosage regimen for at least 2 or more courses before increasing the dose to FOLICULIN HP 150 I.U. per day for 7 - 12 days. As stated above this dose should be followed by HCG 5000 I.U. to 10000 I.U. one day after last dose of FOLICULIN HP. If evidence of ovulation is present but pregnancy is not sure repeat the same dose for 2 more courses. Doses larger than this are not routinely recommended.

**In-vitro Fertilization**:

In-vitro Fertilization therapy with **Foliculin HP** should be initiated in the early follicular phase (cycle day 2 or 3) at a dose of 150 I.U. per day until sufficient Follicular development is attained. In most cases therapy should not exceed beyond 10 days.

**Method of Administration:**

Reconstitute the contents of vial containing FOLICULIN HP in 1ml of Sodium Chloride Injection and administer subcutaneous immediately. Any unused portion of reconstituted solution should be discarded.

## 4.3 Contraindications

FOLICULIN HP is contra indicated in women who exhibit:

1. High levels of FSH, indicating primary ovarian failure.
2. Uncontrolled thyroid or adrental dysfunction.
3. An organic intracranial lesion such as pituitary tumour.
4. The presence of any cause of infertility other than anovulation unless they are candidates for in vitrofertilization.
5. Ovarian cysts or enlargement not due to ovarian polycystic ovarian disease.
6. Prior hypersensitivity to urofollitropin.
7. FOLICULIN HP is contra- indicated in women who are pregnant. There are limited human data on the effect of FOLICULIN HP when administered during pregnancy.

## 4.4 Special Warnings and Precautions for use

FOLICULIN HP should be used by Physician who are thoroughly familiar with infertility problems.

1. FOLICULIN HP should be used only with appropriate monitoring facilities.
2. Lowest dose consistent with expectation of good result should be used.

Ovarian response should be carefully monitored to minimise the risk of over stimulation. If the ovaries are abnormally enlarged on last day of FOLICULIN HP therapy, HCG should not to be administered in this course therapy. This reduces development of OHSS (Ovarian Hyperstimulation Syndrome).

## 4.5 Interaction with other medicinal products and other forms of interaction:

No clinically significate drug/drug or drug/food interactions have been reported during FOLICULIN HP therapy.

### 4.6 Pregnancy and lactation:

FOLICULIN HP should not be given if pregnancy is suspected or to lactating mothers.

### 4.7 Effects on ability to drive and use machines:

No information provided.

### 4.8 Undesirable effects:

In Female, a local reaction at the injection site, Fever and arthralgia have been observed in rare cases.

### 4.9 Overdose:

The effect of an overdose is unknown, nevertheless one could expect ovarian hyper stimulation syndrome to occur.

## 5. PHARMACOLOGICAL CHARACTERISTICS:

### 5.1 Pharmacodynamic properties:

#### 5.1.1 Pharmacology and Mode of Action

Pharmacotherapeutic group: Human follicle stimulating hormone, ATC code: G03GA04

FSH is required for folliculogenesis, it stimulates growth of the preantral follicle, maturation of preantral follicle in preovulatory follicle by bringing about granulose cell aromatase activity and enzymes involved in progesterone biosynthesis. FSH also triggers receptor for luteinizing hormone on granulosa cells that leads to ovulation and development of corpus luteum in response to mid-cycle luteinizing hormone surge. Exogenous FSH stimulation has a specific role in follicular recruitment and dominant follicle selection. In normal ovulatory cycle, increase in FSH levels during luteo-follicular transition phase causes sustained growth of 5 to 10 antral follicle in each ovary. However, the FSH levels decline in response to negative

feedback mechanism of estradiol and inhibin in late follicular stage thus only a single dominant follicle with increased receptivity to FSH grows, and other follicles undergo atresia. Exogenous FSH administration expands the FSH window thus resulting in pool of maturing follicles that attains dominance and do not undergo atresia.

HP-FSH is a highly purified preparation of human follicle stimulating hormone (hFSH) extracted from the urine of postmenopausal women. Human FSH consists of two non-covalently linked glycoproteins designated as α and β subunits. The alpha subunit has 92amino acids of which two are modified by attachment of carbohydrates. The β subunit has 111 amino acids of which two are modified by attachment of carbohydrates.

The primary action of follitropin in women with gonadal dysfunction is the stimulation of follicular development and steroid production. Follitropin may also be used to promote multiple follicular development in medically assisted reproduction programs. In order to induce ovulation, in the absence of an endogenous luteinizing hormone (LH) surge, human chorionic gonadotropin (hCG) must be given after follitropin administration once follicular maturation has occurred.

FSH stimulates the recruitment and growth of early antral follicles by binding to the G protein coupled receptors expressed exclusively on granulosa cells (GCs). An adenylate cyclase-mediated signal is activated, followed by the expression of multiple mRNAs that encode proteins responsible for cell proliferation, differentiation, and function. FSH stimulates GC proliferation and growth (mitogenic action) and induces aromatase activity via P450 activation. Concomitantly, the number of FSH receptors increases as GCs respond to FSH. The regulation of GC FSH receptor activity involves not only a direct cAMP-mediated FSH influence on its own receptor gene but also estrogen and other inhibitory agents, including epidermal growth factor, fibroblast growth factor, and GnRH-like protein. Inhibin and activin, which are also produced by granulosa cells in response to FSH, have autocrine activity and stimulate FSH receptor production, thus enhancing FSH action.

### 5.1.2. Pharmacodynamics Studies

To clarify the pharmacodynamics of urinary gonadotropins, same doses of two different brands of HP FSH (Metrodin -Serono Laboratories, Aubonne, Switzerland or Pergonal -Serono, Rome, Italy) were injected intramuscularly into normal adult men in a crossover manner, and serum follicle-stimulating hormone (FSH) and luteinizing hormone were measured by radioimmunoassay. Follicle-stimulating hormone bioavailability parameters of Metrodin (150

IU), such as peak concentration ($C_{max}$), the time when $C_{max}$ is observed, half-life, and area under concentration, were 8.9 +/- 2.5 mIU/mL, 7.7 +/- 2.1 hours, 36.0 +/- 16.4 hours, and 258.6 +/- 47.9 mIU/mL X hour, respectively, and were not statistically different from those of Pergonal. On the other hand, by daily administration of Metrodin into women with isolated gonadotropin deficiency, serum FSH levels were elevated gradually, reached peak levels within 4 days, and maintained the same levels until the doses were increased. This pattern of FSH accumulation was parallel with the simulation pattern calculated using bioavailability parameters obtained from normal men, suggesting that exogenously administered FSH distributes into peripheral circulation in the manner of a one compartment model.

### 5.1.3. Safety Pharmacology

Lipoprotein (a) [Lp(a)] differs from low density lipoproteins by an additional large protein, apoliprotein(a), disulphide-linked to an apo B-100 apoprotein. [Lp(a)] is a strong independent risk factor both for ischaemic heart disease and for cerebrovascular disease. A prospective, randomized, controlled study compared the effects of recombinant human FSH (r-hFSH) and highly purified urinary FSH (u-hFSH HP) on lipoprotein (a) concentrations in women undergoing ovarian stimulation. Fifty infertile women were randomly allocated into two equally sized treatment groups (n = 25 per group). Thirty normal ovulation women were recruited as controls. The infertile women received u-hFSH or r-hFSH 150 IU/day starting on cycle day 2. From cycle day 6 the dose was adjusted according to ovarian response. Human chorionic gonadotrophin 10,000 IU was administered once there was at least one follicle ≥ 18 mm in diameter. The luteal phase was supported with progesterone 50 mg/day for at least 15 days. Repeated measurements of Lp(a) concentrations were performed during both stimulated and natural cycles. A significant increase in luteal phase Lp(a) concentrations was detected in the stimulated cycles, whereas no significant changes in serum Lp(a) concentrations were observed during natural cycles. There were no significant differences between the urinary and recombinant FSH effects on serum Lp(a). The luteal Lp(a) increase was transitory because after 1 month Lp(a) concentrations returned to baseline values if pregnancy failed to occur; in pregnant women persistent increased Lp(a) concentrations were found at the 8th week. The percentage changes in serum Lp(a) were positively correlated with the luteal progesterone increase ($r = 0.40$, $p < 0.05$), but not with follicular or luteal oestradiol increase. The women with low baseline Lp(a) (≤ 5 mg/dl) had a greater increase of the Lp(a) concentrations at mid-luteal phase than women with baseline Lp(a) >5 mg/dl. In conclusion, urinary hFSH administration does not directly influence Lp(a) concentrations. The luteal Lp(a) increase in

stimulated cycles is not related to gonadotrophin treatment per se, but appears to be related to the high luteal progesterone concentrations, physiologically or pharmacologically determined

### 5.2 Pharmacokinetic properties:

No Pharmacokinetic studies data is available.

### 5.3 Pre-clinical safety data:

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, with recombinant FSH.

The Ames test did not show any mutagenic activity of FSH.

No carcinogenicity study has been performed.

In a fertility study, high doses of recombinant FSH exerted marked pharmacological effects on the ovary and other genital organs resulting in impaired fertility and increased embryo-fetal mortality in the rat and in the rabbit.

FOLICULIN HP was well tolerated locally after subcutaneous administration in a study performed in rabbits.

## 6. PHARMACEUTICAL PARTICULARS:

### 6.1 List of Excipients

- Mannitol
- Sucrose
- Anhydrous Disodium Hydrogen phosphate
- Sodium Ascorbate
- Phosphoric Acid
- Sodium Hydroxide
- Water for Injection

### 1.2 Incompatibility:

The product is stable and there is no incompatibility amongst excipients.

### 6.3 Shelf-life:

36 months from the date of manufacturing.

### 6.4 Storage conditions:

Vials of FOLICULIN HP should store between $2^0$C -$8^0$C.Do not freeze. Protect from light. Reconstituted solution of FOLICULIN HP should be used immediately after preparation. Discard any unused portion

### 6.5 Nature and Contents of the container:

FOLICULIN HP is supplied in vial containing sterile, freeze dried an almost white or slightly yellow powdered cake having FSH activity of 150 I.U. Each vial is accompanied by an ampoule containing 1 ml of Sodium chloride Injection B.P.

### 1.6 Special precautions for disposal

Not applicable

## 7. APPLICANT/MANUFACTURER:

**Applicant:**

Bharat Serums & Vaccines Ltd.

3rd Floor, Liberty Tower, Plot No. K-10,

Behind Reliable Plaza, Kalwa Industrial Estate, Airoli,

Navi Mumbai 400708

**Manufactured by:**

Bharat Serums and Vaccines Limited.

Plot No. K-27, Anand Nagar, Jambivili Village,

Additional M.I.D.C., Ambernath East- 421506,

Maharashtra State, India.