Generic Name Size: 17 pt
Brand Name Size: 15 pt

oestradiol levels and inability to luteinize to a normal ovulatory stimulus. In line with the action of LH activity in enhancing steroidogenesis, oestradiol levels associated with treatment with **IVFhMG** are higher than with recombinant FSH preparations in downregulated IVF/ICSI cycles. This issue should be considered when monitoring patient's response based on oestradiol levels. In the testes, FSH induces the transformation of premature to mature Sertoli cells. It mainly causes the maturation of the seminal canals and the development of the spermatozoa. However, a high concentration of androgens within the testes is necessary and can be attained by a prior treatment using HCG.

5.2 Pharmacokinetic Properties

The pharmacokinetics of **IVFhMG** following intramuscular or subcutaneous administration shows great interindividual variability. After 7 days of repeated dosing with 150 IU **IVFhMG** in downregulated healthy female volunteers, plasma FSH concentrations Cmax (baseline-corrected) (mean ± SD) were 8.9 ± 3.5 IU/L and 8.4 ± 3.2 IU/L for the SC and IM administration, respectively. The area under the curve (AUC) of FSH concentration was (mean ± SD) 180 ± 77 h.IU/L and 166 ± 67 h.IU/L for SC and IM administration, respectively. Maximum FSH concentrations were reached (Tmax) within 7 hours for both routes of administration. After repeated administration, FSH was eliminated with a half-life (T1/2)(mean ± SD) of 30 ± 11 hours and 27 ± 9 hours for the SC and IM administration, respectively. **IVFhMG** is excreted primarily via the kidneys. The pharmacokinetics of **IVFhMG** in patients with renal or hepatic impairment has not been investigated.

6.Non- Clinical Properties

6.1 Animal Toxicology/Pharmacology

Non-clinical data reveal no special hazard for humans, which is not known from the extensive clinical experience. Reproduction toxicity studies have not been carried out to evaluate the effects of **IVFhMG** during pregnancy or postpartum as Menotropin is not indicated during these periods. **IVFhMG** consist of naturally occurring hormones and should be expected to be non-genotoxic. Carcinogenicity studies have not been carried out as the indication is for short term treatment.

7. Description

IVFhMG (Human Menopausal Gonadotrophin,(HMG) is a gonadotrophin extracted from the urine of postmenopausal women. It has both luteinising hormone and follicle stimulating hormone activity in a 1:1 ratio. Human Chorionic Gonadotrophin (HCG), a naturally occurring hormone in postmenopausal urine, is present in **IVFhMG** and is the main contributor of the LH activity.

8. Pharmaceutical Particulars

8.1 Incompatibilities: In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

8.2 Shelf Life: Please see manufacturing date and expiry date printed on the pack. The reconstituted product should be used immediately, and any remaining solution should be discarded. For immediate and single use following reconstitution.

8.3 Package Information :
75 IU - One Vial + Sodium Chloride Injection I.P. 0.9% w/v 2ml

8.4 Storage and Handling Instructions: Store between 2°C to 8°C.
Do not freeze. Store in the original container to protect from light & moisture.

9. Patient Counselling Information: Patient should be counselled on the appropriate usage of **IVFhMG** for Injection with close monitoring on the dosage and administration under sec no. 4.2, undesirable effects under sec no. 4.8, warnings and precautions under sec no. 4.4.

10. Details of Manufacturer: Shree Venkatesh International Ltd

11. Details of Permission or Licence Number : G/28/1808

Manufactured by:
Shree Venkatesh International Ltd
(A WHO-GMP Certified Company)
Block No.311, Kosamba Pardi Road,
Village: Nandav, Taluka: Mangrol ,
Dist: Surat, Pin: 394125.

NEOVA
BIOGENE

Marketed by:
Neova Biogene Pvt Ltd
Monte Plaza,MM Malviya Marg
Mulund(W),Mumbai-80.India.

IN03781800

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

℞

Menotropin For Injection IP 75 IU

IVFhMG 75

Highly Purified I.M./S.C use only.

Combi-Pack Lyophilized.

1. Generic Name: Menotropin for Injection IP 75 IU (Menotropin IP e.q. to activity of Follicle Stimulating Hormones (FSH) ... 75 IU, Luteinizing Hormone (LH) ..... 75 IU)

2. Composition:

Each combipack contains:
(1) Menotropin for Injection IP .....75 IU (Lyophilized)
Each vial contains:
Human Menopausal Gonadotropipn IP .... 75 IU
Excipients.....q.s

(2) Sodium Chloride Injection IP 0.9% w/v. One ampoule of 1 ml
Each ml contains:
Sodium Chloride IP ……0.9 % w/v
Water for injection IP .....q.s.

3. Dosage Form and Strength:IVFhMG is supplied in glass vials containing sterile lyophilized powder equivalent to 75 IU of Menotropin.

4. Clinical Particulars

4.1 Indication

Treatment of female and male infertility in the following groups of patients:
Anovulation, including polycystic ovarian disease (PCOD) in women who have been unresponsive to treatment with clomiphene citrate:

- Women undergoing controlled ovarian hyperstimulation: **IVFhMG** can induce the development of multiple follicles for assisted reproductive technologies (ART) (e.g. in vitro fertilisation/embryo transfer (IVF/ET), gamete intra-fallopiantransfer (GIFT) and intracytoplasmic sperm injection (ICSI)).

- Hypogonadotrophic hypogonadism in men: **IVFhMG** may be given in combination with human chorionicgonadotrophin (e.g. Choragon) for the stimulation of spermatogenesis. Patients with primary testicular failure are usually unresponsive.

4.2 Posology and Method of Administration

Treatment with Menotropin should be initiated under the supervision of a physician experienced in the treatment offertility problems.

Posology

For intramuscular or subcutaneous use. The dosage regimens described below are identical for both forms of administration. There are great inter-individual variations in the response of the ovaries to exogenous gonadotrophins. This makes it impossible to set a uniform dosage scheme. The dosage should, therefore, be adjusted individually depending on the ovarian response. Recommendations about dosage and duration of treatment may change depending on the actual treatment protocol.

Anovulatory infertility: IVFhMG is administered to induce follicular maturation and is followed by treatment with chorionic gonadotrophin to stimulate ovulation and corpus luteum formation. **IVFhMG** therapy should start within the initial 7 days of the menstrual cycle. The recommended initial dose of **IVFhMG** is 75-150 IU daily, which should be maintained for at least 7 days. Based on clinical monitoring (including ovarian ultrasound alone or in combination with measurement of oestradiol levels) subsequent dosing should be adjusted according to individual patient response. Adjustments in dose should not be made more frequently than every 7days. The recommended dose increment is 37.5 IU per adjustment and should not exceed 75 IU. The maximum daily dose should not be higher than 225 IU. If a patient fails to respond adequately after 3 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, administration of **IVFhMG** is stopped. A single injection of 5,000 IU to 10,000 IU of hCG should be given 1 day after the last **IVFhMG** 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 to **IVFhMG** is obtained, treatment should be stopped and hCG withheld and the patient should use a barrier method of contraception or refrain from having coitus until the next menstrual bleeding has started. Treatment should recommence in the next treatment cycle at a dose lower than in the previous cycle.

Women undergoing controlled ovarian hyperstimulation for multiple follicular development for assisted reproductive technologies (ART): In a protocol using down-regulation with a GnRH agonist, **IVFhMG** therapy should start approximately 2 weeks after the start of agonist treatment. In a protocol using down-regulation with a GnRH antagonist, **IVFhMG** therapy should start on day 2 or 3 of the menstrual cycle. The recommended initial dose of **IVFhMG** is 150-225 IU daily for at least the first 5 days of treatment. Based on clinical monitoring (including ovarian ultrasound alone or in combination with measurement of oestradiol levels) subsequent dosing should be adjusted according to individual

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patient response and should not exceed more than 150 IU per adjustment. The maximum daily dose given should not be higher than 450 IU daily and, in most cases, dosing beyond 20 days is not recommended. When a suitable number of follicles have reached an appropriate size a single injection of 5,000 IU up to 10,000 IU hCG should be administered to induce final follicular maturation in preparation for oocyte retrieval. Patients should be followed closely for at least 2 weeks after hCG administration. If an excessive response to **IVFhMG** is obtained treatment should be stopped and hCG withheld and the patient should use a barrier method of contraception or refrain from having coitus until the next menstrual bleeding has started.

Male infertility: Spermatogenesis is stimulated with chorionic gonadotrophin (1000 – 2000 IU two to three times a week) and then **IVFhMG** is given in a dose of 75 or 150 IU units of FSH with 75 or 150 IU units of LH two or three times weekly. Treatment should be continued for at least 3 or 4 months.

Paediatric population: There is no relevant use of **IVFhMG** in the paediatric population.

Elderly: There is no relevant use of Menotropin in the elderly population.

Method of Administration: By intramuscular or subcutaneous use. The powder must be reconstituted immediately with the solvent provided prior to use. In order to avoid the injection of large volumes up to 3 vials of the powder may be dissolved in 1 ml of the solvent provided. Shaking should be avoided. The solution should not be used if it contains particles or if it is not clear.

4.3 Contraindications:

Women and Men

IVFhMG is contraindicated in women and men with:

- Tumours of the pituitary gland or hypothalamus

- Hypersensitivity to the active substance or to any of the excipients

Women

- Ovarian, uterine or mammary carcinoma

- Pregnancy and lactation

- Gynaecological haemorrhage of unknown aetiology

- Ovarian cysts or enlarged ovaries not due to polycystic ovarian disease.

In the following situations treatment outcome is unlikely to be favourable, and therefore **IVFhMG** should not be administered:

- Primary ovarian failure

- Malformation of sexual organs incompatible with pregnancy

- Fibroid tumours of the uterus incompatible with pregnancy

- Structural abnormalities in which a satisfactory outcome cannot be expected, for example, tubal occlusion (unless superovulation is to be induced for IVF), ovarian dysgenesis, absent uterus or premature menopause.

Men

- Tumours in the testes

- Prostate carcinoma

4.4 Special Warnings and Precautions

IVFhMG is a potent gonadotropic 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, and calls for monitoring of ovarian response with ultrasound, alone or in combination with measurement of serum oestradiol levels, on a regular basis. There is considerable inter-patient variability in response to **IVFhMG** administration, with a poor response to **IVFhMG** in some patients. The lowest effective dose in relation to the treatment objective should be used. The first injection of **IVFhMG** 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 tumours, 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 hyperstimulation. Adherence to recommended **IVFhMG** dosage and regimen of administration, and careful monitoring of therapy will minimise the incidence of such events. Acute interpretation of the indices of follicle development and maturation requires a physician who is experienced in the interpretation of the relevant tests.

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. Adherence to recommended **IVFhMG** dosage, regimen of administration and careful monitoring of therapy will minimise the incidence of ovarian hyperstimulation and multiple pregnancy. Patients undergoing controlled ovarian hyperstimulation may be at an increased risk of developing hyperstimulation in view of the excessive oestrogen response and multiple follicular development. In ART, aspiration of all follicles prior to ovulation may reduce the occurrence of hyperstimulation. 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 severity 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 hospitalised and specific therapy for OHSS started.

Multiple pregnancy

Multiple pregnancy, especially high order, carries an increased risk of adverse maternal and perinatal outcomes. In patients undergoing ovulation induction with gonadotrophins, the incidence of multiple pregnancies is increased compared with natural conception. The majority of multiple conceptions are twins. To minimise the risk of multiple pregnancy, 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 age of the patient. The patient 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 ART procedures than 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 treatment. The prevalence of ectopic pregnancy after IVF has been reported to be 2 to 5%, as compared to 1 to 1.5% 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 if treatment with gonadotrophins increases the baseline risk of these tumours 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

Women with generally recognised risk factors for thromboembolic events, such as personal or family history, severe obesity (Body Mass Index > 30kg/m2) or thrombophilia may have an increased risk of venous or arterial thromboembolicevents, during or following treatment with gonadotrophins. 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 thromboembolic events

4.5 Drug Interactions

No interaction studies have been performed with **IVFhMG** In humans.Although there is no controlled clinical experience, it is expected that the concomitant use of **IVFhMG** and clomiphene citrate may enhance the follicular response. When using GnRH agonist for pituitary desensitization, a higher dose of **IVFhMG** may be necessary to achieve adequate follicular response.

4.6 Use in Special Population

Fertility

Menotropin is indicated for use in infertility.

Pregnancy

IVFhMG is contraindicated in women who are pregnant. There are no or limited amount of data from the use of **IVFhMG** in pregnant women. No animal studies have been carried out to evaluate the effects of **IVFhMG** during pregnancy.

Breast - feeding

Menotropin is contraindicated in women who are breast-feeding.

4.7 Effect on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. However, **IVFhMG** is unlikely to have influence on the patient's ability to drive and use machines.

4.8 Undesirable Effects

The most frequently reported adverse drug reactions (ADR) during treatment with **IVFhMG** in clinical trials are Ovarian Hyperstimulation Syndrome OHSS, abdominal pain, headache, abdominal distension, and injection site pain.

4.9 Overdose

The effects of an overdose is unknown, nevertheless one could expect ovarian hyperstimulation syndrome to occur.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Menotropin (HMG) directly affects the ovaries and the testes. HMG has a gametropic and steroidogenic effect. In the ovaries, the FSH-component in HMG induces an increase in the number of growing follicles and stimulates their development. FSH increases the production of oestradiol in the granulosa cells by aromatising androgens that originate in the Theca cells under the influence of the LH-component. Follicular growth can be stimulated by FSH in the total absence of LH, but the resulting follicles develop abnormally and are associated with low

25 mm