1.7 Summary of Product Characteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT

MENOTAS HP 150

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MENOTAS HP 150
Each vial contains:
Menotropin BP equivalent to activity of
Follicle Stimulating Hormone 150 IU
Luteinising Hormone 150 IU
Excipients: Q.S.
Reconstitute with 1 ml of Sodium Chloride Injection BP (0.9% w/v)

3. PHARMACEUTICAL FORM

Powder for injection; and solvent for parenteral use.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Women:
- Anovulation, including polycystic ovarian disease (PCOD), in women who have been unresponsive to treatment with clomiphene citrate.
- Controlled ovarian hyperstimulation to induce the development of multiple follicles for assisted reproductive technologies (ART)

Selection of Patients
1. A thorough gynecologic and endocrinologic evaluation, including an assessment of pelvic anatomy must be performed before treatment with Menotropin. Patients with tubal obstruction should receive Menotropin only if enrolled in an IVF program.
2. Primary ovarian failure should be excluded by the determination of gonadotrophin levels.
3. Careful examination should be made to rule out the presence of an early pregnancy.
4. Patients in late reproductive life have a greater predilection to endometrial carcinoma as well as a higher incidence of anovulatory disorders. A thorough diagnostic evaluation should always be performed in patients who demonstrate abnormal uterine bleeding or other signs of endometrial abnormalities before starting Menotropin therapy.
5. Evaluation of the partner's fertility potential should be included in the workup.

Men:
Hypogonadotrophic hypogonadism in men: Menotropin with concomitant human chorionic gonadotropins therapy is indicated for the stimulation of spermatogenesis in men who have primary or secondary hypogonadotrophic hypogonadism.

4.2 Posology and method of administration

Dosage

Anovulatory infertility:

The dosage and schedule of treatment must be determined according to the needs of each patient. Response is monitored by studying the patient's serum estradiol levels and vaginal ultrasound visualization of follicles. Menotropin for injection may be given daily which should be maintained for 7 days by subcutaneous or intramuscular injection to provide a dose of 75 to 150 IU/day, and gradually adjusted if necessary until an adequate response is achieved, followed after 1 day by human chorionic gonadotropins. In menstruating patients, treatment should be started on the 4th/5th day of the menstrual cycle. The treatment course should be abandoned if no response is seen. Once adequate follicular development is evident, administration of Menotropin is stopped, and ovulation may then be induced by administering human chorionic gonadotropins (hCG) at a dose of 5000 -10000 IU. The administration of hCG must be withheld in cases where the ovaries are abnormally enlarged on the last day of therapy. This should reduce the chance of developing ovarian hyperstimulation syndrome (OHSS).

Assisted Reproductive Technologies

The recommended initial dose of Menotropin for injection for patients who have received a GnRH agonist for pituitary suppression is 150 to 300 IU/day. Based on clinical monitoring (including serum estradiol levels and vaginal ultrasound results) subsequent dosing should be adjusted according to individual patient response. Adjustments in dose should not be made more frequently than once every two days and should not exceed 150 IU per adjustment. The maximum daily dose of Menotropin for injection given should not exceed 450 IU.

Once adequate follicular development is evident, hCG should be administered to induce final follicular maturation in preparation for oocyte retrieval. The administration of hCG must be withheld in cases where the ovaries are abnormally enlarged on the last day of therapy.

This should reduce the chance of developing OHSS.

Hypogonadotrophic hypogonadism in men

Spermatogenesis is stimulated with chorionic gonadotropins (1000 – 2000 IU two to three times a week) and then Menotropin for injection is given in a dose of 75 or 150 IU two or three times weekly. Treatment should be continued for at least 3 or 4 months.

Administration

Reconstitute with 1ml of Sodium Chloride Injection BP (0.9% w/v) provided in this pack and administer subcutaneously or intramuscularly immediately. Any unused reconstituted material should be discarded. Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration, whenever solution and container permit

4.3 Contraindications

Men and Women

1. Tumours of the pituitary or hypothalamic glands
2. Hypersensitivity to the active substance or any of the excipients used in the formulation

Women who have:

1. A high FSH level indicating primary ovarian failure.
2. Uncontrolled thyroid and adrenal dysfunction.
3. An organic intracranial lesion such as a pituitary tumor.
4. Sex hormone dependent tumors of the reproductive tract and accessory organs.
5. Abnormal uterine bleeding of undetermined origin.
6. Ovarian cysts or enlargement not due to polycystic ovary syndrome.
7. Menotropin for injection is not indicated in women who are pregnant. There are limited human data on the effects of Menotropin when administered during pregnancy.

Men

1. Tumours in the testes
2. Patients primary testicular failure are usually unresponsive to Menotropin and hCG therapy.
3. Prostate carcinoma

4.4 Special warnings and special precautions for use

Menotropin for injection is a drug that should only be used by physicians who are thoroughly familiar with infertility problems. It is a potent gonadotropic substance capable of Ovarian Hyperstimulation Syndrome (OHSS) in women with or without pulmonary or vascular complications. Gonadotrophin therapy requires a certain time commitment by physicians and supportive health professionals, and its use requires the availability of appropriate monitoring facilities.

Overstimulation of the ovary during Menotropin therapy

Ovarian Enlargement: Mild to moderate uncomplicated ovarian enlargement which may be accompanied by abdominal distension and/or abdominal pain occurs in approximately 5 to 10 % of women treated with Menotropin and hCG, and generally regresses without treatment within two or three weeks. The lowest dose consistent with expectation of good results and careful monitoring

of ovarian response can further minimize the risk of overstimulation.
If the ovaries are abnormally enlarged or the serum estradiol concentration is excessively elevated on the last day of Menotropin for injection therapy, hCG should not be administered in this course of treatment; this will reduce the chances of development of the Ovarian Hyperstimulation Syndrome (OHSS). In the event of hyperstimulation, the patient should refrain from sexual intercourse or to use barrier contraception methods for at least 4 days.
OHSS: OHSS is a medical event distinct from uncomplicated ovarian enlargement. OHSS may progress rapidly to become a serious medical event. It is characterized by an apparent dramatic increase in vascular permeability which can result in a rapid accumulation of fluid in the peritoneal cavity, thorax, and potentially, the pericardium. The early warning signs of development of OHSS are severe pelvic pain, nausea, vomiting, and weight gain.The following symptomatology has been seen with cases of OHSS: abdominal pain, abdominal distension, gastrointestinal symptoms including nausea, vomiting and diarrhea, severe ovarian enlargement, weight gain, dyspnea, and oliguria. Clinical evaluation may reveal hypovolemia, hemoconcentration, electrolyte imbalances, ascites, hemoperitoneum, pleural effusions, hydrothorax, acute pulmonary distress, and thromboembolic events.
Transient liver function test abnormalities suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on liver biopsy, have been reported in association with the OHSS.
A physician experienced in the management of the syndrome, or who is experienced in the management of fluid and electrolyte imbalances, should be consulted.

Pulmonary and Vascular Complications

Serious pulmonary conditions (e.g. atelectasis, acute respiratory distress syndrome) have been reported. In addition, thromboembolic events both in association with, and separate from, the OHSS have been reported following Menotropin therapy. In women with generally recognised risk factors for thromboembolic events, such as personal or family history, treatment with gonadotropins may further increase the risk.

Multiple Pregnancies

The patient and her partner should be advised of the potential risk of multiple births before starting treatment.
Pregnancy wastage: Pregnancy wastage by miscarriage is higher in patients undergoing stimulation of follicular growth for ART procedures than in the normal population. 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.

4.5 Interaction with other medicinal products and other forms of interaction

No drug/drug interaction studies have been conducted with Menotropin in humans.

4.6 Pregnancy and lactation

Menotropin should not be given during pregnancy. It is Pregnancy Category X drug. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if Menotropin are administered to a nursing woman.

4.7 Effects on ability to drive and use machines

None known

4.8 Undesirable effects

The adverse events occurring at an incidence of > 2 % in women treated with Menotropin are listed as below.
Body as a whole: Abdomen enlarged, Abdominal cramps, Abdominal fullness, Abdominal pain, Headache, Injection site pain, Injection site reaction, Malaise, Pain.
Digestive: Constipation, Diarrhea, Nausea, Vomiting, Nervous System: Dizziness
Respiratory: dysponea
Urogenital: Breast tenderness, Hot flash, OHSS, Pelvic discomfort, Post retrieval pain. Very rare cases of allergic reactions, localised or generalised, and hypersensitivity have been reported after treatment with gonadotropin containing products

4.9 Overdosage

The acute toxicity of menotrophin has been shown to be very low. However, too high a dosage for more than one day may lead to hyperstimulation, which is categorised as mild, moderate or severe. Symptoms of overdosage usually appear 3 - 6 days after treatment with human chorionic gonadotrophin.
Mild hyperstimulation - Symptoms include some abdominal swelling and pain, ovaries enlarged to about 5cm diameter. Therapy - rest; careful observation and symptomatic relief. Ovarian enlargement declines rapidly.
Moderate hyperstimulation - Symptoms include more pronounced abdominal distension and pain, nausea, vomiting, occasional diarrhoea, ovaries enlarged up to 12cm diameter. Therapy - bed rest; close observation especially in the case of conception occurring, to detect any progression to severe hyperstimulation.
Pelvic examination of enlarged ovaries should be gentle in order to avoid rupture of the cysts. Symptoms subside spontaneously over 2 - 3 weeks.
Severe hyperstimulation - This is a rare but serious complication - symptoms include pronounced abdominal distension and pain, ascites, pleural effusion, decreased blood volume, reduced urine output, electrolyte imbalance and

sometimes shock, ovaries enlarge to in excess of 12cm diameter. Therapy - hospitalisation; treatment should be conservative and concentrate on restoring blood volume and preventing shock. Acute symptoms subside over several days and ovaries return to normal over 20 - 40 days if conception does not occur - symptoms may be prolonged if conception occurs.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Menotrophin is a gonadotrophin extracted from the urine of postmenopausal women and having both luteinising hormone and follicle stimulating hormone activity. It is given by intramuscular or subcutaneous injection in the treatment of male and female infertility.

Menotrophin (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.

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

HMG is not effective when taken orally and is injected either intramuscularly or subcutaneously. The biological effectiveness of HMG is mainly due to its FSH content. The pharmacokinetics of HMG following intramuscular or subcutaneous administration show great individual variation. The maximum serum level of FSH is reached approximately 18 hours after intramuscular injection and 12 hours after subcutaneous injection. After that, the serum level decreases by a half-life of approximately 55 hours following intramuscular administration and 50 hours following subcutaneous administration.

Excretion of HMG, following administration, is predominantly renal.

5.3 Preclinical safety data

Toxic effects caused by HMG are unknown in humans.

There is no evidence of teratogenic, mutagenic or carcinogenic activity of HMG. Antibodies against HMG can be built up in single cases following repeated cyclical administration of HMG, causing the treatment to be ineffectual.

6.0 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Dibasic potassium phosphate
Potassium dihydrogen phosphate

6.2 Incompatibilities

None known.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store between 2°C to 8°C.
Keep the container in the outer carton in order to protect from light.
Do not refrigerate or Freeze.

6.5 Nature and contents of container

Each box of MENOTAS HP 150 contains one Vial of sterile freeze-dried Menotropin 150 IU & one ampoule containing 1 ml of Sodium Chloride Injection (0.9% w/v) BP as solvent.

6.6 Instruction for use / handling

Use immediately after reconstitution.
Discard unused material

7.0 MARKETING AUTHORISATION HOLDER

Intas Pharmaceutical Limited
Corporate House, Near Sola Bridge, S.G. Highway,
Thaltej, Ahmedabad-380054, Gujarat, INDIA

8.0 MARKETING AUTHORISATION NUMBER

XXX

9.0 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Not applicable

10.0 DATE OF REVISION OF THE TEXT

XXX