SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<TRADE NAME> 75 IU, powder and solvent for solution for injection
<TRADE NAME> 150 IU, powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains freeze-dried powder with 75 IU human follicle stimulating hormone activity (FSH) and 75 IU human luteinising hormone activity (LH).
Human menopausal Gonadotrophin (HMG) is extracted from urine of post-menopausal women. Human Chorionic Gonadotrophin (hCG), extracted from urine of pregnant women, is added to contribute to the total LH activity.

Each vial contains freeze-dried powder with 150 IU human follicle stimulating hormone activity (FSH) and 150 IU human luteinising hormone activity (LH).
Human menopausal Gonadotrophin (HMG) is extracted from urine of post-menopausal women. Human Chorionic Gonadotrophin (hCG), extracted from urine of pregnant women, is added to contribute to the total LH activity.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Powder in vial: white to almost white lyophilized powder
Solvent in pre-filled syringe: clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ovulation induction: for the induction of ovulation in amenorrhoeic or anovulatory women who have not responded to treatment with clomiphene citrate.

Controlled ovarian hyperstimulation (COH) within a medically assisted reproduction technology (ART): induction of multiple follicular development in women undergoing assisted reproduction techniques such as in vitro fertilization (IVF).

4.2 Posology and method of administration

Posology

Treatment with <TRADE NAME> should be initiated under the supervision of a physician experienced in the treatment of infertility problems.

There are great inter- and intra-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. This requires ultrasonography and may also include monitoring of oestradiol levels.

Females with anovulation:

The objective of a treatment with <TRADE NAME> is to develop a single mature de Graaf follicle from which the ovum will be released after the administration of human chorionic gonadotrophin (hCG).

<TRADE NAME> can be administered by daily injection. In menstruating patients the treatment should begin within the first 7 days of the menstrual cycle.

A commonly used regimen starts at 75 to 150 IU of FSH per day and is increased if necessary by 37.5 IU (up to 75 IU), with intervals of 7 or 14 days preferably, in order to achieve an adequate but not excessive response.

Maximum daily dosages of HMG <TRADE NAME> should generally not exceed 225 IU.

The treatment should be adjusted to the individual patient's response, assessed by measuring the follicle size by ultrasonography and/or oestrogen levels.

The daily dose is then maintained until pre-ovulatory conditions are reached. Usually, 7 to 14 days of treatment is sufficient to reach this state.

The administration of <TRADE NAME> is then discontinued and ovulation can be induced by administering human chorionic gonadotrophin (hCG).

If the number of responding follicles is too high or oestradiol levels increase too rapidly, i.e. more than a daily doubling for oestradiol for two or three consecutive days, the daily dose should be decreased. Since follicles of over 14 mm may lead to pregnancies, multiple pre-ovulatory follicles exceeding 14 mm carry the risk of multiple gestations. In that case hCG should be withheld and pregnancy should be avoided in order to prevent multiple gestations. The patient should use a barrier method of contraception or refrain from having coitus until the next menstrual bleeding has started (see section 4.4). The treatment should recommence in the next treatment cycle at a lower dose than in the previous cycle.

If a patient fails to adequately respond after 4 weeks of treatment, the cycle should be abandoned and the patient should recommence at a higher initial dose than in the previous cycle.

Once the ideal response is obtained, a single injection of 5 000 IU to 10 000 IU of hCG should be administered 24 to 48 hours after the last <TRADE NAME> injection.

The patient is recommended to have coitus on the day of hCG injection and the following day.

Alternatively, intrauterine insemination may be performed.

Females undergoing ovary stimulation for induction of multiple follicular development – as part of assisted reproductive technology:

Pituitary down-regulation in order to suppress the endogenous LH peak and to control basal levels of LH is now commonly achieved by administration of a gonadotrophin releasing hormone agonist (GnRH agonist) or gonadotrophin releasing hormone antagonist (GnRH-Antagonist).

In a commonly used protocol the administration of <TRADE NAME> begins approximately two weeks after the start of the agonist treatment, both treatments are then continued until adequate follicular development has been achieved. For example, following two weeks of pituitary down-regulation with agonist, 150 to 225 IU of <TRADE NAME> are administered for the first five-seven days. The dose is then adjusted according to the patient's ovarian response.

An alternative protocol for controlled ovarian hyperstimulation involves the administration of 150 to 225 IU of <TRADE NAME> daily starting on the 2nd or 3rd day of the cycle. The treatment is continued until sufficient follicular development has been achieved (assessed by monitoring of serum oestrogen concentrations and/or ultrasound) with the dose adjusted according to the patient's response (usually not higher than 450 IU daily). Adequate follicular development is usually achieved on average around the tenth day of treatment (5 to 20 days).

When an optimal response is obtained a single injection of 5 000 IU to 10 000 IU of hCG administered 24 to 48 hours after the last <TRADE NAME> injection, to induce final follicular maturation.

Oocyte retrieval is performed 34-35 hours later.

Paediatric population

The medicine is not intended for paediatric use.

Method of administration

<TRADE NAME> is intended for subcutaneous and intramuscular administration.

The powder should be reconstituted immediately prior to use with the solvent provided.

To prevent painful injections and minimize leakage from the injection site <TRADE NAME> should be slowly administered subcutaneously. The subcutaneous injection site should be alternated to prevent lipo-atrophy. Any unused solution should be discarded.

Subcutaneous injections can be self-administered by the patient, provided the physician's instructions and recommendations are strictly followed.

4.3 Contraindications

- Hypersensitivity to Menotrophin or to any of the excipients
- Ovarian enlargement or cysts not related to polycystic ovarian syndrome
- Gynaecological bleeding of unknown cause
- Ovarian, uterine or breast carcinoma
- Tumours of the hypothalamus or pituitary gland

<TRADE NAME> is contraindicated when an effective response cannot be achieved, for example:

- Primary ovarian failure
- Malformations of sexual organs incompatible with pregnancy
- Fibroid tumours of the uterus incompatible with pregnancy

4.4 Special warnings and precautions for use

Anaphylactic reactions may occur, particularly in patients with known hypersensitivity to gonadotropins. The first injection of <TRADE NAME> should be always performed under direct medical supervision and in settings with facilities for cardio-pulmonary resuscitation.

The first injection of <TRADE NAME> should be performed under direct medical supervision.

Self-injections of <TRADE NAME> should be performed only by motivated, trained and well informed patients. Prior to self-injections, the patient must be shown how to perform a subcutaneous injection, showing her where the injection can be given and how to prepare the solution to be injected.

Before starting the 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, for which appropriate specific treatments are given.

Ovarian hyperstimulation syndrome (OHSS)
Ultrasonographic assessment of follicular development, and determination of oestradiol levels should be performed prior to treatment and monitored at regular intervals during treatment. This is particularly important at the beginning of the stimulation (see below). Apart from the development of a high number of follicles, oestradiol levels may rise very rapidly, e.g. more than a daily doubling for two or three consecutive days, and possibly reaching excessively high values. The diagnosis of ovarian hyperstimulation may be confirmed by ultrasound examination. If this unwanted ovarian hyperstimulation occurs (i.e. not as part of controlled ovarian hyperstimulation in medically assisted reproduction programs), the administration of <TRADE NAME> should be discontinued. In that case

pregnancy should be avoided and hCG must be withheld, because it may induce, in addition to multiple ovulation, the ovarian hyperstimulation syndrome (OHSS). Clinical symptoms and signs of mild ovarian hyperstimulation syndrome are abdominal pain, nausea, diarrhoea, and mild to moderate enlargement of ovaries and ovarian cysts. In rare cases severe ovarian hyperstimulation syndrome occurs, which may be life-threatening. This is characterised by large ovarian cysts (prone to rupture), ascites, often hydrothorax and weight gain. In rare instances, venous or arterial thromboembolism may occur in association with OHSS (see section 4.8).

Multiple Pregnancies
In patients undergoing ART procedures the risk of multiple pregnancies is related mainly to the number of replaced embryos. In patients undergoing a treatment for ovulation induction the incidence of multiple pregnancies and births is increased as compared to natural conception. The majority of multiple conceptions are twins. To minimise the risk of multiple pregnancy, careful monitoring of ovarian response is recommended.

Pregnancy wastage
The incidence of spontaneous miscarriage is higher in patients treated with FSH than in the general population, but it is comparable to the incidence found in women with other fertility disorders.

Ectopic pregnancy
Since infertile women undergoing assisted reproduction, and particularly IVF, often have tubal abnormalities the incidence of ectopic pregnancies might be increased. Early ultrasound confirmation that a pregnancy is intrauterine is therefore important.

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 gonadotropins 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 > 30 kg/m2) or thrombophilia, may have an increased risk of venous or arterial thromboembolic events, during or following treatment with gonadotrophins. In these women, the benefits of gonadotrophin administration need to be weighed against the risks (see section 4.8).

Additional information

This medicine contains less than 1 mmol of sodium (23 mg) per reconstituted solution, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No drug/drug interaction studies have been conducted for <TRADE NAME> in humans. Although there is no clinical experience, it is expected that the concomitant use of <TRADE NAME> 75-150 IU and clomiphene citrate may enhance the follicular response. When using GnRH agonist for pituitary desensitisation, a higher dose of <TRADE NAME> 75-150 IU may be necessary to achieve adequate follicular response

4.6 Fertility, pregnancy and lactation

Pregnancy
<TRADE NAME> should not be used during pregnancy.
No teratogenic risk has been reported following controlled ovarian stimulation in clinical use with urinary gonadotrophins. To date, no other relevant epidemiological data are available. Animal studies do not indicate teratogenic effect.

Lactation
<TRADE NAME> should not be used during lactation.
During lactation the secretion of prolactin can entail a poor response to ovarian stimulation.

4.7 Effects on ability to drive and use machines

<TRADE NAME> is unlikely to have influence on the patient's performance to drive and use machines.

4.8 Undesirable effects

The most relevant occurring adverse drug reaction in clinical trials with <TRADE NAME> is (dose-related) ovarian hyperstimulation (OHSS), generally mild with small ovarian enlargement, abdominal discomfort or pain. Only one case of OHSS was serious.

The most frequent adverse reactions with <TRADE NAME> were headache and abdominal distension as well as nausea, fatigue, dizziness and pain at the injection site

The table below displays the main adverse drug reactions (>1%) in women treated with <TRADE NAME> in clinical trials according to body system and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Within each system organ class, the ADRs are ranked under headings of frequency, most frequent reactions first, using the following convention:

Very common (≥ 1/10); common (≥1/100 to ≤1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated form the available data).

Body System*	Frequency	Adverse Drug Reaction
Nervous system disorders	Very common Common	Headache Dizziness
Gastro-intestinal disorders	Very common Common	Abdominal distension Abdominal discomfort, Abdominal pain, Nausea
Musculoskeletal and connective tissue disorders	Common	Back pain, Sensation of heaviness
Reproductive system and breast disorders	Common	Ovarian hyperstimulation syndrome, Pelvic pain, Breast tenderness
General disorders and Application site disorders	Common	Pain at injection site, Injection site reaction, Fatigue, Malaise, Thirst
Vascular disorders	Common	Hot flushing

*The most appropriate MedDRA term is listed to describe a certain reaction; synonyms or related conditions are not listed, but should be taken into consideration as well.

From published studies, the following adverse reactions have been seen in patients treated with human menopausal gonadotrophins.

*Severe ovarian hyperstimulation (OHSS) with marked ovarian enlargement and cyst formation, acute abdominal pain, ascites, pleural effusion, hypovolaemia, shock and thromboembolic disorders. (see also section 4.4)

* Ovarian torsion, usually in association with severe cases of OHSS

* Rupture of ovarian cysts with intraperitoneal haemorrhage, fatal outcomes of cyst rupture have been reported.

*Allergic reactions also with generalised symptoms have been reported after treatment with gonadotrophin containing products. (see also section 4.4)

Local reactions at the site of injection such as pain, redness, bruising, swelling and/or irritation are expected AE following administration of gonadotrophins.

The frequency of such events are expected to be higher with the intramuscular than with the subcutaneous administration.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [to be completed nationally].

4.9 Overdose

No data on acute toxicity of Menotrophin in humans is available, but the acute toxicity of urinary gonadotrophin preparations in animal studies has been shown to be very low. Too high a dosage of Menotrophin may lead to hyperstimulation of the ovaries (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Gonadotrophins.
ATC CODE: G03GA02
The active substance in <TRADE NAME> is highly purified human menopausal gonadotrophin.
The FSH activity in <TRADE NAME> is obtained from urine of post-menopausal women; the LH activity is obtained both from urine of post-menopausal women and urine of pregnant women. The preparation is standardised to have a FSH/LH activity ratio of approximately 1.

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.

5.2 Pharmacokinetic properties

The biological effectiveness of Menotrophin is mainly due to its FSH content. The pharmacokinetics of Menotrophin following intramuscular or subcutaneous administration shows great inter-individual variability. According to data collected from the studies performed with Menotrophin, after a single injection of 300 IU, the maximum serum level of FSH is reached approximately 19 hours after intramuscular injection and 22 hours after subcutaneous injection. FSH peak concentrations reached 6.5 ±2.1 IU/L with an AUC0-t of 438.0 ± 124.0 IUxh/L after i.m. administration. After sc administration, Cmax reached 7.5 ±2.8 IU/L with an AUC0-t of 485.0 ± 93.5 IUxh/L.
AUC and Cmax levels for LH resulted to be significantly lower in the s.c. group compared to the i.m group. This result may be due to very low levels detected (close to or below the detection limits) in both groups and to a great intra- and inter-individual variability.

After that, the serum level decreases by a half-life of approximately 45 hours following intramuscular administration and 40 hours following subcutaneous administration. Excretion of Menotrophin, following administration, is predominantly renal.

No pharmacokinetic studies were performed in patients with impaired hepatic or renal function.

5.3 Preclinical safety data

No non-clinical studies have been performed with <TRADE NAME>.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder: lactose monohydrate
Solvent: sodium chloride and water for injection

6.2 Incompatibilities

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

6.3 Shelf life

2 years.
After reconstitution, immediate use is recommended.

6.4 Special precautions for storage

Do not store above 25°C. Keep the vial and the prefilled syringe of solvent in the outer carton, in order to protect from light.

6.5 Nature and contents of container

1 set contains: Powder in a vial (type I glass), sealed with a rubber closure and held in place with a flip-off cap (aluminium and coloured plastic: 75 IU light green, 150 IU dark green) + 1 ml of solvent in a prefilled syringe (type I glass), fitted with a tip cap (isoprene and bromobutyl) and plunger stopper (Chlorobutyl with silicone) + 1 needle for the reconstitution and intramuscular injection and 1 needle for the subcutaneous injection. These 4 elements are packed in a blister (PVC); pack size of 1, 5 and 10 sets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The solution must be prepared just before injection.

Each vial is for single use only. The medicinal product must be reconstituted under aseptic conditions.

<TRADE NAME> must only be reconstituted with the solvent provided in the package.

A clean preparation area should be prepared and hands should first be washed before the solution is reconstituted.

Set out all the following items on the clean surface:
- two cotton-wool swabs moistened with alcohol (not provided)
- one vial containing <TRADE NAME> powder
- one prefilled syringe with solvent
- one needle for preparing the injection and for the intramuscular injection
- a fine bore needle for subcutaneous injection

Reconstitution of the powder for solution for injection

Prepare the solution for injection:

Remove the cap from the prefilled syringe, insert the reconstitution needle (long needle) on the syringe.

1. Remove the aluminium capsule cover from the vial containing <TRADE NAME> powder and disinfect the rubber area of the cap with a cotton-wool swab moistened with alcohol
2. Take the syringe and slowly inject the solvent into the powder vial through the rubber cap.
3. Gently roll the vial between the hands until the powder is completely dissolved, taking care to avoid creating foam.
4. Once the powder is dissolved (which, in general, occurs immediately), slowly draw the solution into the syringe.

When reconstituting more than 1 vial of <TRADE NAME>, draw back the reconstituted contents of the first vial into the syringe and slowly inject into a second vial after repeating the step 1 to 4.

If multiple vials of powder are used, the amount of menotrophin contained in 1 ml of reconstituted solution will be as follows:

<TRADE NAME> 75 IU powder and solvent for solution for injection	
Number of vials used	Total amount of menotrophin in 1 ml of solution
1	75 IU
2	150 IU

3	225 IU
4	300 IU
5	375 IU
6	450 IU

<TRADE NAME> 150 IU powder and solvent for solution for injection	
Number of vials used	Total amount of menotrophin in 1 ml of solution
1	150 IU
2	300 IU
3	450 IU

The solution must be clear and colourless.

Dispose of all used items:

Any unused product or waste material should be disposed of in accordance with local requirements (once the injection is ended, all the needles and empty syringes should be disposed of in an appropriate container).

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT