Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Menotrophin Ferring 600 IU solution for injection in a pre-filled pen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled multidose pen delivers highly purified menotrophin (human menopausal gonadotrophin, HMG) corresponding to follicle stimulating hormone activity FSH 600 IU and luteinizing hormone activity LH 600 IU in 0.96 mL solution.

One mL of solution contains 625 IU FSH activity and 625 IU LH activity.

Human Chorionic Gonadotrophin (hCG), a naturally occurring hormone in postmenopausal urine, is present in Menotrophin Ferring and is the main contributor of the LH activity.

The active ingredient in Menotrophin Ferring is obtained from the urine of postmenopausal women.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled pen (injection).

Clear solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Menotrophin Ferring is indicated for the treatment of infertility in the following clinical situations:

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) (e.g. in vitro fertilisation/embryo transfer (IVF/ET), gamete intra-fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)).

4.2 Posology and method of administration

Treatment with Menotrophin Ferring should be initiated under the supervision of a physician experienced in the treatment of fertility problems.

Posology

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. Menotrophin Ferring can be given alone or in combination with a gonadotrophin-releasing hormone (GnRH) agonist or antagonist. Recommendations about dosage and duration of treatment may change depending on the actual treatment protocol.

Women with anovulation (including PCOD)

The object of Menotrophin Ferring therapy is to develop a single Graafian follicle from which the oocyte will be liberated after the administration of human chorionic gonadotrophin (hCG).

Menotrophin Ferring therapy should start within the initial 7 days of the menstrual cycle. The recommended initial dose of Menotrophin Ferring 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 7 days. 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 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 to 10,000 IU hCG should be given 1 day after the last Menotrophin Ferring 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 Menotrophin Ferring is obtained treatment should be stopped and hCG withheld (see section 4.4) and the patient should use a barrier method of contraception or refrain from having coitus until the next menstrual bleeding has started.

Women undergoing controlled ovarian hyperstimulation for multiple follicular development for assisted reproductive technologies (ART)
In a protocol using down-regulation with a GnRH agonist, Menotrophin Ferring therapy should start approximately 2 weeks after the start of the agonist treatment. In a protocol using down-regulation with a GnRH antagonist, Menotrophin Ferring therapy should start on day 2 or 3 of the menstrual cycle. The recommended initial dose of Menotrophin Ferring 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 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 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 Menotrophin Ferring is obtained treatment should be stopped and hCG withheld (see section 4.4) and the patient should use a barrier method of contraception or refrain from having coitus until the next menstrual bleeding has started.

Renal/hepatic impairment
Patients with renal and hepatic impairment have not been included in clinical trials (see section 5.2).

Paediatric population
There is no relevant use of Menotrophin Ferring in the paediatric population.

Method of administration
Menotrophin Ferring is intended for subcutaneous (S.C.) injection, preferably in the abdominal wall. The first injection should be performed under direct medical supervision. Patients must be educated on how to use the Menotrophin Ferring injection pen and to perform injections. Self-administration should only be performed by patients who are well motivated, adequately trained and have access to expert advice.

For instructions on the administration with the pre-filled pen, see the "Instructions for Use" supplied in the package with the pen.

4.3 Contraindications

Menotrophin Ferring is contraindicated in women who have:

- Tumours of the pituitary gland or hypothalamus
- Ovarian, uterine or mammary carcinoma
- Pregnancy and lactation
- Gynaecological haemorrhage of unknown aetiology
- Hypersensitivity to the active substance or any of the excipients listed in section 6.1
- Ovarian cysts or enlarged ovaries not due to polycystic ovarian disease.

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

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

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Menotrophin Ferring 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, and calls for monitoring of ovarian response with ultrasound, alone or preferably in combination with measurement of serum oestradiol levels, on a regular basis. There is considerable inter-patient variability in response to menotrophin administration, with a poor response to menotrophin in some patients. The lowest effective dose in relation to the treatment objective should be used.

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 Menotrophin Ferring 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.

The following symptoms may be observed in severe cases of OHSS: abdominal pain, abdominal distension, severe ovarian enlargement, weight gain, dyspnoea, oliguria and gastrointestinal symptoms including nausea, vomiting and diarrhoea. Clinical evaluation may reveal hypovolaemia, haemoconcentration, electrolyte imbalances, ascites, haemoperitoneum, pleural effusions, hydrothorax, acute pulmonary distress, and thromboembolic events.

Excessive ovarian response to gonadotrophin treatment seldom gives rise to OHSS unless hCG is administered to trigger ovulation. Therefore, in cases of ovarian hyperstimulation it is prudent to withhold hCG and advise the patient to refrain from coitus or to use barrier methods for at least 4 days. OHSS may progress rapidly (within 24 hours to several days) to become a serious medical event, therefore patients should be followed for at least two weeks after the hCG administration.

Adherence to recommended Menotrophin Ferring dosage, regimen of administration and careful monitoring of therapy will minimise the incidence of ovarian hyperstimulation and multiple pregnancy (see sections 4.2 and 4.8). 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.

This syndrome occurs with higher incidence in patients with polycystic ovarian disease.

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 tumors 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/m^2) 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. It should be noted however, that pregnancy itself also carries an increased risk of thromboembolic events.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Menotrophin Ferring in humans.

Although there is no controlled clinical experience, it is expected that the concomitant use of Menotrophin Ferring and clomiphene citrate may enhance the follicular response. When using GnRH agonist for pituitary desensitisation, a higher dose of Menotrophin Ferring may be necessary to achieve adequate follicular response.

4.6 Fertility, pregnancy and lactation

Pregnancy
Menotrophin Ferring is contraindicated in women who are pregnant (see section 4.3).
There are no or limited amount of data from the use of menotrophins in pregnant women. No animal studies have been carried out to evaluate the effects of Menotrophin Ferring during pregnancy (see section 5.3).

Breastfeeding
Menotrophin Ferring is contraindicated in women who are lactating (see section 4.3).

Fertility
Menotrophin Ferring is indicated for use in infertility (see section 4.1).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most serious and frequently reported adverse drug reactions reported during treatment with Menotrophin Ferring in clinical trials are OHSS, abdominal pain, headache, abdominal distension and injection site pain, with an incidence rate up to 5%. The table below displays the main adverse drug reactions in women treated with Menotrophin Ferring in clinical trials distributed by system organ classes (SOCs) and frequency. Further, the ADRs seen during post-marketing experience are mentioned with unknown frequency.

System Organ Class	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**	**Unknown**
Eye disorders				Visual disorders [a]
Gastrointestinal disorders	Abdominal pain, Abdominal distension, nausea, enlarged abdomen	Vomiting, Abdominal discomfort, Diarrhoea		
General disorders and administration site condition	Injection site reactions [b]	Fatigue		Pyrexia, Malaise
Immune system disorders				Hypersensitivity reactions [c]
Investigations				Weight increased
Musculoskeletal & connective tissue disorders				Musculoskeletal pain [d]
Nervous system disorders	Headache	Dizziness		
Reproductive system disorders	OHSS [e], pelvic pain [f]	Ovarian cyst, Breast complaints [g]		Ovarian torsion [e]
Skin and subcutaneous tissue disorders			Acne, Rash	Pruritus, Urticaria
Vascular disorders		Hot flush		Thromboembolism [e]

[a] Individual cases of temporary amaurosis, diplopia, mydriasis, scotoma, photopsia, vitreous floaters, vision blurred and vision impairment have been reported as visual disorders during the post-marketing period.
[b] Most frequently reported injection site reaction was injection site pain.
[c] Cases of localised or generalised allergic reactions, including anaphylactic reaction, along with associated symptomatology have been reported rarely.
[d] Musculoskeletal pain includes arthralgia, back pain, neck pain and pain in extremities.
[e] Gastrointestinal symptoms associated with OHSS such as abdominal distension and discomfort, nausea, vomiting and diarrhoea have been reported with Menotrophin Ferring in clinical trials. In cases of severe OHSS ascites and pelvic fluid collection, pleural effusion, dyspnoea, oliguria, thromboembolic events and ovarian torsion have been reported as rare complications.

[f] Pelvic pain includes ovarian pain and adnexa uteri pain.
[g] Breast complaints include breast pain, breast tenderness, breast discomfort, nipple pain and breast swelling.

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 HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

The effect of an overdose is unknown, nevertheless one could expect ovarian hyperstimulation syndrome to occur (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Gonadotrophins, ATC code: G03G A02

Menotrophin Ferring is produced from the urine of postmenopausal women. Human Chorionic Gonadotrophin (hCG), a naturally occurring hormone in postmenopausal urine, is present in Menotrophin Ferring and is the main contributor of the LH activity.

Menotrophin, which contains both FSH and LH activity, induces ovarian follicular growth and development as well as gonadal steroid production in women who do not have primary ovarian failure. FSH is the primary driver of follicular recruitment and growth in early folliculogenesis, while LH is important for ovarian steroidogenesis and is involved in the physiological events leading to the development of a competent pre-ovulatory follicle. Follicular growth can be stimulated by FSH in the total absence of LH, but the resulting follicles develop abnormally and are associated with low oestradiol levels and inability to luteinize to a normal ovulatory stimulus.

In line with the action of LH activity in enhancing stereoidogenesis, oestradiol levels associated with treatment with Menotrophin Ferring 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. The difference in oestradiol levels is not found when using low-dose ovulation induction protocols in anovulatory patients.

5.2 Pharmacokinetic properties

The pharmacokinetic profile of the FSH in Menotrophin Ferring has been documented. After 7 days of repeated dosing with 150 IU Menotrophin Ferring in downregulated healthy female volunteers, maximum plasma FSH concentrations (baseline-corrected) (mean ± SD) were 8.9 ± 3.5 IU/L and 8.5 ± 3.2 IU/L for the SC and IM administration, respectively. Maximum FSH concentrations were reached within 7 hours for both routes of administration. After repeated administration, FSH was eliminated with a half-life (mean ± SD) of 30 ± 11 hours and 27 ± 9 hours for the SC and IM administration, respectively. Although the individual LH concentration versus time curves show an increase in the LH concentration after dosing with Menotrophin Ferring, the data available were too sparse to be subjected to a pharmacokinetic analysis.

Menotrophin is excreted primarily via the kidneys.

The pharmacokinetics of Menotrophin Ferring in patients with renal or hepatic impairment has not been investigated.

5.3 Preclinical safety data

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 Menotrophin Ferring during pregnancy or postpartum as Menotrophin Ferring is not indicated during these periods.
Menotrophin Ferring 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Phenol
Methionine
Arginine hydrochloride
Polysorbate 20
Sodium hydroxide
Hydrochloric acid
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

3 years

In-Use: 28 days.
Store below 25 °C when in-use.

In-use stability has been demonstrated for 28 days at 25°C. Therefore, once opened, the product may be stored for a maximum of 28 days below 25°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.

Always store the pen with the pen cap on, in order to protect from light.

For storage conditions after first use of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Multidose cartridge (Type I glass) with a plunger (rubber) and a crimp cap (aluminium) with bi-layer septum (rubber). Each cartridge contains 0.96 mL of solution.
Pack size of 1 pre-filled pen and 12 injection needles (stainless steel).

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

The solution should not be administered if it contains particles or is not clear.

The instructions for use of the pen must be followed. Discard used needles immediately after injection.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Ferring Ireland Ltd
United Drug House
Magna Drive, Magna Business Park
Citywest Road
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1009/030/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of authorisation: 4th November 2022
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10 DATE OF REVISION OF THE TEXT