SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

FOSTIMON 150 IU, powder and solvent for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 150 IU of urofollitropin (follicle-stimulating hormone FSH): 1 ml of reconstituted solution contains either 150 IU, 300 IU or 450 IU of urofollitropin when respectively 1, 2, or 3 vials are reconstituted in 1 ml of solvent.

The specific *in vivo* activity is equal or superior to 5000 IU of FSH per mg of protein.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.
The powder is white to off-white and the solvent is clear and colourless.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Sterility in women:

- Anovulation (including polycystic ovarian syndrome, PCOS) in women who have been unresponsive to treatment with clomifene citrate.
- Controlled ovarian hyperstimulation to induce the development of multiple follicles in Assisted Reproductive Technologies (ART) such as *in vitro* fertilisation (IVF), Gamete Intra-fallopian Transfer (GIFT) and Zygotes Intra-fallopian Transfer (ZIFT).

4.2 Posology and method of administration

Posology

Treatment with Fostimon 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 gonadotropins. 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.

- Anovulation (including PCOS):

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

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 Fostimon is then discontinued and ovulation can be induced by administering human chorionic gonadotropin (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.

Maximum daily dosages of FSH should generally not exceed 225 IU.

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 Fostimon injection.
The patient is recommended to have coitus on the day of hCG injection and the following day.
Alternatively, intrauterine insemination may be performed.

- Controlled ovarian hyperstimulation during ART

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 gonadotropin releasing hormone agonist (GnRH agonist).

In a commonly used protocol the administration of Fostimon 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 FSH are

administered for the first seven days. The dose is then adjusted according to the patient's ovarian response.

An alternative protocol for superovulation involves the administration of 150 to 225 IU of FSH 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 Fostimon injection, to induce final follicular maturation.
Oocyte retrieval is performed 34-35 hours later.

Method of administration
Fostimon is intended for intramuscular or subcutaneous 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 Fostimon should be slowly administered intramuscularly or 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 FSH 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

FOSTIMON 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

Self-injections of Fostimon 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. The first injection of Fostimon should be performed under direct medical supervision.
Particularly, in patients with known hypersensitivity to gonadotropins anaphylactic reactions might occur. In these patients, the first injection of Fostimon should be performed by a physician in settings with facilities for cardio-pulmonary resuscitation.

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.

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.

Unwanted ovarian hyperstimulation
In the treatment of female patients, ultrasonographic assessment of follicular development, and determination of oestradiol levels should be performed prior to treatment and at regular intervals during treatment. 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 Fostimon 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).

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

Infectious diseases
When medicinal products prepared from human urine are administered, the possibility of transmitting infective agents cannot be totally excluded.
This also applies to unknown or emerging viruses and other pathogens.
However, this risk is limited by the extraction/purification process, which includes viral inactivation/removal steps. These steps have been validated using model viruses, and particularly HIV, *Herpes virus* and *Papillomavirus*.

Up to now there is reassuring clinical experience with follitropin products regarding the lack of virus transmission associated with the administration of gonadotropins extracted from human urine.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No drug/drug interaction studies have been conducted for Fostimon in humans. Although there is no clinical experience, it is expected that the concomitant use of Fostimon and clomifene citrate may enhance the follicular response.

4.6 Fertility, pregnancy and lactation

Pregnancy

Fostimon is not indicated during pregnancy and lactation.

No teratogenic risk has been reported following controlled ovarian stimulation, in clinical use with urinary gonadotropins. To date no other relevant epidemiological data are available.

Animal studies do not indicate teratogenic effect.

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

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

4.8 Undesirable effects

Adverse reactions (ADRs) reported in clinical trials with Fostimon are listed in the table below by body system and frequency. Most events were of mild to moderate severity.

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).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

For other undesirable effects which may be associated with the use of gonadotropins such as FSH, see section 4.4.

MedDRA System Organ Class	**Frequency**	**Adverse Drug Reaction (MedDRA Preferred term)**
Endocrine disorders	Uncommon	Hyperthyroidism
Psychiatric disorders	Uncommon	Mood swings
Nervous system disorders	Common	Headache
	Uncommon	Lethargy Dizziness
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea Epistaxis
Gastro-intestinal disorders	Common	Constipation Abdominal distension
	Uncommon	Nausea Abdominal pain Dyspepsia
Skin and subcutaneous tissue disorders	Uncommon	Erythema Pruritus
Renal and urinary disorders	Uncommon	Cystitis
Reproductive system and breast disorders	Common	Ovarian hyperstimulation syndrome
	Uncommon	Breast enlargement Breast pain Hot flush
General disorders and administration site conditions	Common	Pain
	Uncommon	Fatigue
Investigations	Uncommon	Bleeding time prolonged

Local reactions at the site of injection (pain, redness and haematoma) have been rarely observed.

In rare cases, arterial and venous thromboembolism have been associated with a treatment with human menotrophins/chorionic gonadotropins.
The incidence of miscarriage with gonadotropins therapy is comparable to the incidence in women with other fertility disorders. A slightly increased risk of ectopic pregnancy and multiple gestations has been observed.

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 the national reporting system detailed below:

UNITED KINGDOM: Yellow Card Scheme. Website:

www.mhra.gov.uk/yellowcard

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Gonadotropins
ATC CODE: G03GA04
The active substance in Fostimon is highly purified Follicle Stimulating Hormone (FSH), obtained from human Menopausal Gonadotropin (HMG). The main effect of a FSH injection is the development and maturation of de Graaf follicles.

5.2 Pharmacokinetic properties

After subcutaneous injection of 300 IU of Fostimon, C_{max} is 5.74 ± 0.95 IU/l, and T_{max} is 21.33 ± 9.18 hours. $AUC_{0-\infty}$ is 541.22 ± 113.83 IU/l×hour, which is approximately the double of that described in the literature after intramuscular administration of 150 IU uFSH: 258.6 ± 47.9 IU/lxhour (measurements of FSH plasmatic contents by RIA assays).

Elimination half-life is about 50 hours.
After intramuscular injection, literature reports that the bioavailability of FSH is about 70%.
The pharmacokinetics of FSH 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 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.
Fostimon was well tolerated locally after subcutaneous administration in a study performed in rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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 ampoule in the outer carton, in order to protect from light.

6.5 Nature and contents of container

Powder in a vial (type I glass), with a stopper (bromobutylrubber), with a seal (aluminium) and a flip-off cap (plastic) + 1 ml of solvent in an ampoule (type I glass); pack size of 1, 5 and 10 sets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The solution must be prepared just before injection.

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

FOSTIMON must only be reconstituted with the solvent provided in the package.

A clean surface 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 alcohol swabs (not provided)

- one vial containing FOSTIMON powder

- one solvent ampoule

- one syringe (not provided)

- one needle for preparing the injection (not provided)

- fine bore needle for subcutaneous injection (not provided)

Both intramuscular and subcutaneous routes of administration are possible. If the intramuscular route is preferred appropriate needles will have to be prescribed.

<u>Reconstitution of the solution for injection using 1 vial of powder</u>

1.Open the solvent ampoule containing the clear liquid.

A coloured mark is indicated on the tip of the solvent ampoule:

At this mark the ampoule neck is specifically designed to break more easily. Gently tap the top of the ampoule to dislodge any liquid which may remain in the tip. Firmly press the ampoule above the neck and break it while levering up at the coloured mark. Carefully place the opened ampoule onto the preparation area.

Withdraw the solvent:

Attach the reconstitution needle (long needle) to the syringe. With the syringe in one hand, hold the previously opened solvent ampoule, place the needle into it and withdraw all the solvent. Place the syringe very carefully on the preparation area and avoid touching the needle.

Presentations other than ampoules (prefilled syringe) should be considered for self-administration by patients, for example Fostimon PFS.

Prepare the solution for injection:

2.Remove the coloured plastic cap from the powder vial by gently pushing it upwards. Disinfect the top of the rubber stopper by wiping it with an alcohol swab and allow to dry.

3 – Pick up the syringe and slowly inject the solvent into the powder vial through the middle of the top of the rubber stopper. Press the plunger down firmly to squirt all the solution onto the powder. Do not shake, but 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:

With the needle still inserted, turn the vial upside down.

Make sure the needle tip is underneath the level of the liquid.

Gently push the plunger to draw all the solution up into the syringe.

Check that the reconstituted solution is clear and colourless.

Preparation of higher doses, using more than 1 vial of powder

When reconstituting more than 1 vial of Fostimon, at the end of step 4 above, draw the reconstituted contents of the first vial back into the syringe, and slowly inject into a second vial. Repeat steps 2 to 4 for the second and subsequent vials and until the contents of the required number of vials equivalent to the prescribed dosage are dissolved (within the limit of the maximum total dosage of 450 IU, corresponding to a maximum of 6 vials of Fostimon 75 IU or 3 vials of Fostimon 150 IU).

The solution must be clear and colourless.

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 ampoules should be disposed of in an appropriate container).

7 MARKETING AUTHORISATION HOLDER

IBSA Farmaceutici Italia S.r.l
Via Martiri di Cefalonia 2,
26900 Lodi - Italy

8 MARKETING AUTHORISATION NUMBER

PL 21039/0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/06/2025

10 DATE OF REVISION OF THE TEXT

12/06/2025