PURIFICATION PROCESS

Highly Purified Human FSH[1]

IBSA

Caring Innovation

Lamone Plant, Switzerland

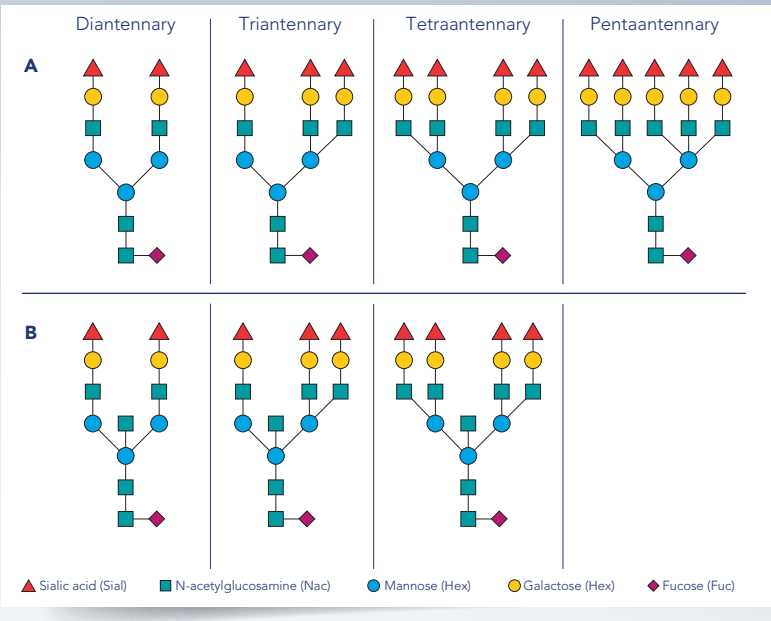
At IBSA, quality is the challenge

IBSA is an international pharmaceutical company headquartered in Lugano, Switzerland, active **since 1945** in the **manufacturing and marketing of drugs for human use**.

IBSA has established dedicated plants and a unique, global patented in-house **process for the purification of urinary gonadotrophins starting from human donors**.[1] These hormones are released according to the **highest purity and safety standards**, while preserving the intact structure of the proteins.[2]

FSH isoforms and the importance of the purification process

The follicle-stimulating hormone (FSH) is a major player in folliculogenesis and oocyte maturation.[3]
FSH is a complex glycoprotein, existing as a family of isoforms, which differ in their ionic charge due to a great variance in their oligosaccharide structure.[4]



Adapted from fig. 1 ref. 1

Extractive FSH

There is a specific pattern of release of different FSH isoforms during women's reproductive life.[1]
It is well known that **with aging the ovary produces increasing amounts of FSH, with increased levels of glycosylation**.
During menopause, almost all circulating FSH is highly glycosylated and thus more acidic.[1,5]
The glycosylation and thus the content of sialic acid in FSH isoforms prevents hepatic degradation of the carbohydrate moiety, conferring higher bioavailability to FSH and allowing higher circulating levels of the molecule.[6,7]

Thus, the extractive FSH used by IBSA, being produced by human cells and obtained from urines of menopausal women, is rich in glycosylated (acidic) FSH isoforms.[1,2]

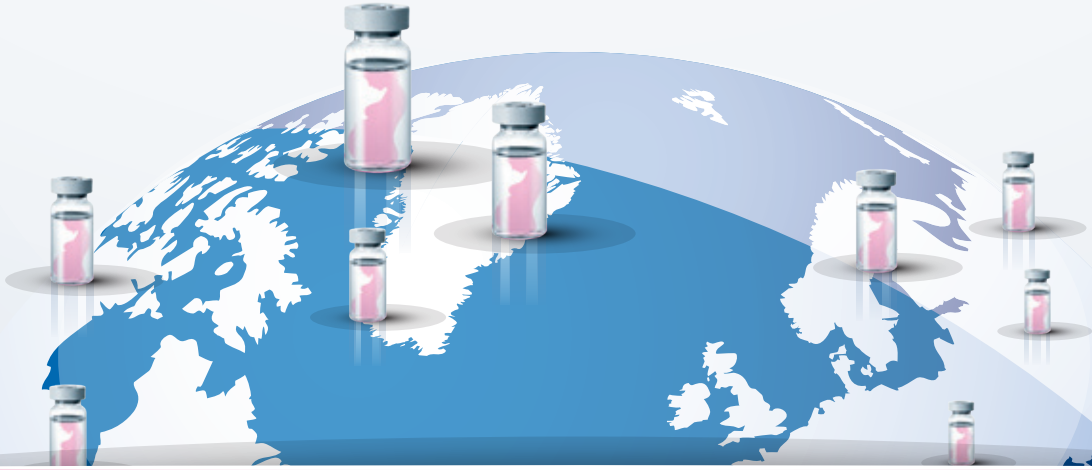
However, there are two main variables that influence the glycosylation content in the final FSH products: the type of raw material to be purified and the purification process.[8]
For IBSA, the challenge is to maintain high purity and quality, while preserving glycosylation in an adequate balance.[2]

Adapted from text from ref. 2

PROCESS SUMMARY

110˙000

vials of 75 IU



Leveraging on state-of-the-art technology and full awareness of the structure-function correlates of gonadotrophins, IBSA developed an entirely new, patented purification process aiming to obtain both the highest purity and a full range of gonadotrophin molecular species.[2]

URINE COLLECTION

FROM ABOUT 100˙000 DONORS

300˙000 L
the **batch size** generated by urine collection

1. Medical check and qualification for donors' pool

- Enrolment of post-menopausal women
- Screening of general health status and of any pathological condition
- Routinary check of the health status of the donors

2. Daily door-to-door collection

- Daily collection of overnight urine
- Specific training for a correct urine collection
- Compensation on a monthly basis, independently from the quantity

3. Rapid quality check

- Quality check of each single urine donation

4. Delivery of collected urine at IBSA plant

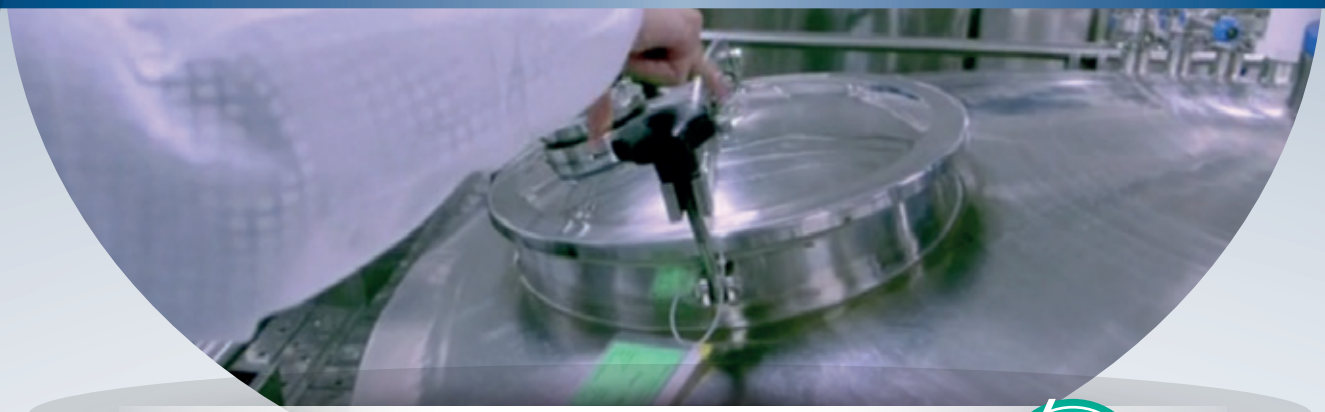
- Real time delivery
- More extensive quality control

5. Urine addressed to purification

- All urines enter the process within a few hours from collection

SOLVENT TREATMENTS
FOR CONTAMINANT ELIMINATION

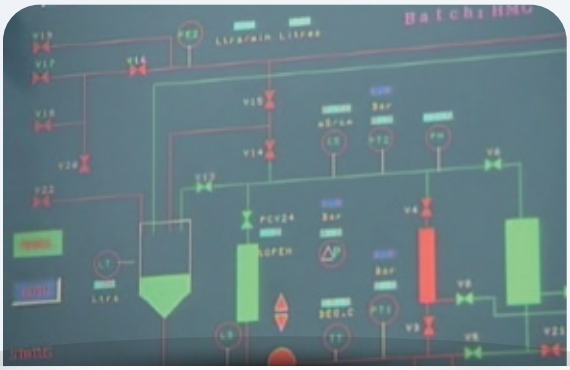
300'000 L



6. Selective precipitation in alkaline bath

VALIDATED VIRUS CLEANING STEP

First treatment of urines at pH 11:
- precipitation of small urinary molecules
- inactivation of viruses potentially present



7. Ultrafiltration

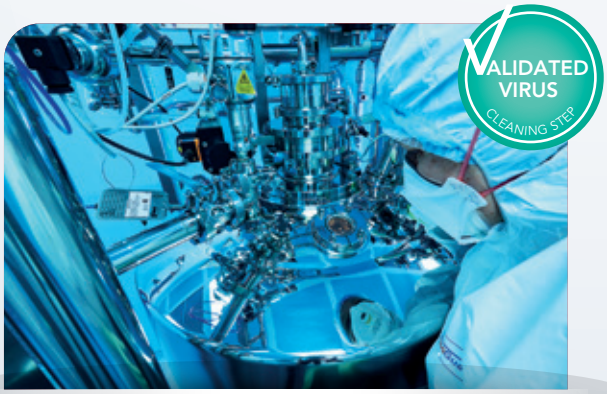
Recovery and ultrafiltration of the supernatant:
- concentration of the solution
- elimination of the small urinary molecules

VALIDATED VIRUS CLEANING STEP

8. Selective precipation in ethanol

- Elimination of some categories of viruses potentially present
- Elimination of the smallest urinary molecules

~ 3 kg



VALIDATED VIRUS CLEANING STEP

9. Drying with acetone and ethanol solubilisation

- Further viral cleaning

10. Early chromatography steps

- Elimination of urinary proteins other than FSH

~ 900 g

INTERMEDIATE QUALITY CHECKS

11. Safety control of release and check list of viruses (HIV, HBV, HCV)

12. Crude extract airshipped to Lamone, Switzerland

13. QC controls for admission into the plant

- Only qualified material is allowed to be processed

CHROMATOGRAPHY STEPS

~ 900 g

14. 1st chromatography step

VALIDATED VIRUS CLEANING STEP

Massive elimination of urinary components:
- removal of the largest part of the urinary proteins

15. 2nd chromatography step

- Clear-cut separation of the residual urinary impurities and recovery of very pure FSH fractions preserving all the FSH isoforms, including the very acidic ones
- Delivery of a comprehensive "human-type" range of FSH isoforms

16. 3rd chromatography step

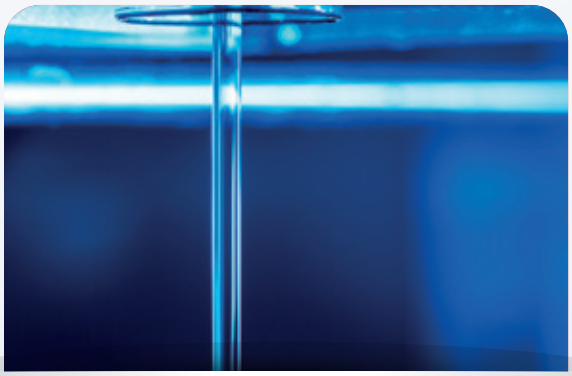
Elimination of last traces of luteinising activity:
- final removal of residual LH/hCG, still present at low concentration at this stage
- further elimination of urinary proteins

~ 1 g

NANOFILTRATION
FOR VIRAL CLEANING

17. The nanofiltration system allows an efficient clearance of potential viruses

Efficient separation of potential residual viruses from FSH ensuring:
- maximum clearing from any tested viral species
- maximum clearing from prions



18. FSH virtually free from potential viruses

FSH purity and specific activity are very high and preserve the original glycosylation of the molecules.

DRUG SUBSTANCE QUALITY CHECKS

~ 1 g

IBSA highly purified human FSH is available for manufacturing of drug products

- Potency
- Purity
- Range of isoforms
- .....

110'000 vials of 75 IU

marketed worldwide

110'000 vials

Summary of product characteristics

1. NAME OF THE MEDICINAL PRODUCT

Meriofert®75 IU, powder and solvent for solution for injection
Meriofert®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 Meriofert® 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 Meriofert® is to develop a single mature de Graaf follicle from which the ovum will be released after the administration of human chorionic gonadotrophin (hCG).

Meriofert® 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 Meriofert® 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 Meriofert® 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 Meriofert® 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 Meriofert® 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 Meriofert® 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 Meriofert® 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 Meriofert® injection, to induce final follicular maturation.

Oocyte retrieval is performed 34-35 hours later.

Paediatric population
The product is not intended for paediatric use.

Method of administration
Meriofert® 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 Meriofert® should be slowly administered subcutaneously. The subcutaneous injection site should be alternated to prevent lipoatrophy. 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

Meriofert® 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 Meriofert® should be always performed under direct medical supervision and in settings with facilities for cardio-pulmonary resuscitation.

The first injection of Meriofert® should be performed under direct medical supervision.

Self-injections of Meriofert® 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 Meriofert® 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 Meriofert® in humans. Although there is no clinical experience, it is expected that the concomitant use of Meriofert® 75-150 IU and clomiphene citrate may enhance the follicular response. When using GnRH agonist for pituitary desensitisation, a higher dose of Meriofert® 75-150 IU may be necessary to achieve adequate follicular response.

4.6 Fertility, pregnancy and lactation
Pregnancy
Meriofert® 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
Meriofert® 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
No studies on the effects on the ability to drive and use machines have been performed.
However, Meriofert® 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 Meriofert® 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 Meriofert® 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 Meriofert® 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 ovar-ian 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 the Italian Medicines Agency Website: https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse.

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 Meriofert® is highly purified human menopausal gonadotrophin.
The FSH activity in Meriofert® is obtained from urine of post-menopausal women; the LH activity is obtained both from urine of post-menopausal women and urine of preg-nant 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 Meriofert®.

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.

Meriofert® 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 Meriofert® 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 Meriofert® 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 Meriofert®, 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:

Meriofert® 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

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

8. MARKETING AUTHORISATION NUMBER(S)
AIC. n. 043275015 -"75 UI powder and solvent for solution for injection" 1 glass vial of powder + 1 pre-filled syringe of solvent + 2 needles
AIC. n. 043275027 -" 75 UI powder and solvent for solution for injection" 5 glass vials of powder + 5 pre-filled syringes of solvent + 10 needles
AIC. n. 043275039 -"75 UI powder and solvent for solution for injection" 10 glass vials of powder + 10 pre-filled syringes of solvent + 20 needles
AIC. n. 043275041 -"150 UI powder and solvent for solution for injection" 1 glass vial of powder + 1 pre-filled syringe of solvent + 2 needles
AIC. n. 043275054 -"150 UI powder and solvent for solution for injection" 5 glass vials of powder + 5 pre-filled syringes of solvent + 10 needles
AIC. n. 043275066 -"150 UI powder and solvent for solution for injection" 10 glass vials of powder + 10 pre-filled syringes of solvent + 20 needles

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorization: May 25, 2015
Date of most recent renewal: January 15, 2020

10. DATE OF REVISION OF THE TEXT
10/07/2021

11. CONDITIONS OF PRESCRIPTION AND DISPENSING
Medicinal product subject to medical prescription (RR)

12. PACKAGING AND CLASSIFICATION FOR REFUNDABILITY
- 75 IU powder and solvent for solution for injection for subcutaneous and intramuscular use" 1 glass vial of powder + 1 pre-filled syringe of solvent + 2 needles. Class A, note 74, Retail price € 26.57
- "75 IU powder and solvent for solution for injection for subcutaneous and intramuscular use" 5 glass vials of powder + 5 pre-filled syringes of solvent + 10 needles. Class A, note 74, Retail price € 132.87
- "150 IU powder and solvent for solution for injection for subcutaneous and intramuscular use" 1 glass vials of powder + 1 pre-filled syringe of solvent + 2 needles. Class A, note 74, Retail price € 53.14
- "150 IU powder and solvent for solution for injection for subcutaneous and intramuscular use" 5 glass vials of powder + 5 pre-filled syringes of solvent + 10 needles. Class A, note 74, Retail price € 265.72

Summary of product characteristics

1. NAME OF THE MEDICINAL PRODUCT

FOSTIMON® 75 IU/1 ml powder and solvent for solution for injection
FOSTIMON® 150 IU/1 ml powder and solvent for solution for injection
FOSTIMON® 225 IU/1 ml powder and solvent for solution for injection
FOSTIMON® 300 IU/1 ml powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains: urofollitropin, corresponding to a highly purified human urinary follicle-stimulating hormone (FSH).
Each vial of 75, 150, 225, 300 contains 75 IU, 150 IU, 225 IU, 300 IU of urofollitropin in powder.

Excipient with known effect: lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Female sterility

- Induction of ovulation, in combination with chorionic gonadotropin, in patients suffering from polycystic ovarian syndrome; amenorrhea or anovulation due to follicular phase deficiency; other sterility conditions associated to an increased LH/FSH ratio.
- FOSTIMON induces the development of multiple follicles in women undergoing induction of ovulation in In Vitro Fertilization programs (IVF) and other Assisted Reproductive Technologies (FIVET-GIFT-ZIFT).

Male sterility
Induction of spermatogenesis in men suffering from hypogonadotropic hypogonadism, in combination with human chrorionic gonadotropin (hCG).

4.2 Posology and method of administration

Posology
Doses and therapy duration shall be adjusted by a doctor according the necessity of each patient.
The dosing schemes reported below are recommended for the following therapeutic indications.

Women with hypothalamus-pituitary gland malfunction associated with oligomennorrhea or amenorrhea
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 gonadotrophin (hCG).
The treatment should begin within the first 7 days of the menstrual cycle and can be administered by daily injection. The treatment should be adjusted to the individual patient's response, assessed by measuring the follicle size by ultrasonography and/or oestrogen levels.

A commonly used regimen starts with 75 to 150 IU of FOSTIMON per day and is increased or decreased, if necessary, by 37.5 IU (up to 75 IU), at intervals of 7 or 14 days preferably, in order to achieve an adequate but not excessive response.
If the patient's response is not adequate after 4 weeks of treatment, the cycle shall be discontinued.
Once the ideal response is obtained, it is necessary to administer up to 10,000 IU of hCG 24-48 hours after the last injection of FOSTIMON.
It is advisable to have sexual intercourses on the day of administration of hCG and on the following day.
If an excessive response is obtained, the treatment will be discontinued and the administration of hCG will not be given (see section 4.4). The following cycle will start with a lower dose.

Stimulation of superovulation in In Vitro Fertilization programs (IVF) and other Assisted Reproductive Technologies.
Administer 150-225 IU of FOSTIMON a day, starting from the 2° or 3° day of the menstrual cycle.
The dose will be adjusted according to the individual response up to a maximum of 450 IU per day, until an adequate follicular development is achieved, assessed by monitoring of oestrogen concentration and/or
ultrasonography.
The final follicular maturation is induced by 10,000 IU of chorionic gonadotropin (hCG) in a single administration, 24-48 hours after the last injection of FOSTIMON.
Pituitary down-regulation in order to suppress the endogenous LH peak and to control basal levels of LH is commonly achieved by administration of GnRH agonists.
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.
A dosing scheme could be: 225 IU of FOSTIMON (s.c. or i.m.) for the first 7 days with the dose then adjusted according to the ovarian response.

Men with hypogonadotropic hypogonadism
Pre-treatment: hCG 2,000 IU i.m. or s.c. twice a week (adjusted to the patient), until the testosterone serum levels are normalised.
Treatment: FOSTIMON 150 IU, one vial i.m. or s.c. thrice a week in combination with hCG 2,000 IU i.m. or s.c. twice a week (or at the dose required to normalise the serum level of testosterone), for 4 months, that could possible become 18 months, according to the prescription of the doctor in case of failure of therapeutic response.

Method of administration
FOSTIMON can be administered by intramuscular or subcutaneous injection.
The solution to be injected shall be prepared immediately before use by dissolving the powder into the solvent provided in the package.
FOSTIMON can be administered immediately after the reconstitution.
Up to 5 vials of product can be solved in 1 ml of solvent, to avoid the administration of large volumes.
See section 6.6 for the direction on reconstitution and dilution of the medicine before administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

In women
FOSTIMON is contraindicated during pregnancy and lactation, 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 also contraindicated when an effective response cannot be achieved, due to primary ovarian failure, malformations of sexual organs incompatible with pregnancy, fibroid tumours of the uterus incompatible with pregnancy.

In men
FOSTIMON is contraindicated in men when an effective response cannot be achieved, as in primary testicular failure.

4.4 Special warnings and precautions for use

FOSTIMON can cause local reactions at the injection site.

Women
Before starting the treatment with FOSTIMON, the couple's infertility should be assessed as appropriate and

possible 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.
Even though following the recommended doses of FOSTIMON minimize the risk of ovarian hyperstimulation, the possibility of hyperstimulation and multiple ovulation shall be considered and monitored during the treatment.
This syndrome can develop in a serious clinical event characterised by large cysts prone to rupture.
A significant hyperstimulation due to an excessive oestrogen response can be avoided if hCG is not administered to induce ovulation. In these cases the patient should not be given hCG and be advised not to have sexual intercourse for at least 4 days.
The patients undergoing superovulation show a higher risk of hyperstimulation due to an excessive oestrogen response and to multiple follicular development. The aspiration of all follicles prior to ovulation can reduce the occurrence of hyperstimulation.
In patients undergoing ART procedures the risk of multiple pregnancies is related mainly to the number of replaced oocytes/embryos. In other patients the incidence of multiple pregnancies and births is increased by FOSTIMON, as by other products inducing ovulation, but the majority of multiple conceptions are twins.
The incidence of spontaneous miscarriage is higher than in the general population, but it is comparable to the incidence found in women with other fertility disorders. In patients not undergoing superovulation, the possible presence of small secondary follicles in association with a dominant follicle visible by ultrasound scan is considered related to a higher incidence of hyperstimulation.

Men
High levels of endogenous FSH suggest a primitive testicular failure. Those patients do not respond to therapy with FOSTIMON/hCG.
An analysis of seminal fluid is recommended 4-6 months after the treatment is started to assess the response.

Important information on excipients
This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, as the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Rare reactions of allergic kind for which an intolerance to lactose was suspected, but not ascertained, were reported. It is important to consider the possible effect of lactose in case of administration to sensitive patients.

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

4.5 Interaction with other medicinal products and other forms of interaction

During the treatment with FOSTIMON no unfavourable interactions were reported. The concomitant use of FOSTIMON with other ovulation stimulants may potentiate the follicular response, whereas the concurrent of a GnRH agonist, inducing pituitary desensitisation, may increase the dose of FOSTIMON required to achieve an adequate ovarian response.
No incompatibility was reported between Fostimon and other drugs.
Fostimon must not be mixed with other drugs in the same syringe.

4.6 Fertility, Pregnancy and Lactation

FOSTIMON is not indicated during pregnancy and lactation.

4.7 Effects on ability to drive and use machines

Attention, vigilance and normal abilities are not affected by the administration of FOSTIMON.

4.8 Undesirable effects

Adverse reactions are classified according to the MedDRA system organ classes and to frequency. Frequency categories are: 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).

MedDRA System Organ Class	Adverse Drug Reaction
Nervous system disorders	
Common:	Headache
General disorders and administration site conditions	
Very common:	Local reactions at the site of injection (mild to moderate level; e.g. pain, erythema, haematoma, petechiae, swelling and/or rash at the injection site)
WOMEN	
Vascular disorders	
Very rare:	Thromboembolism
Reproductive system and breast disorders	
Very common:	Ovarian cyst
Common:	Ovarian Hyperstimulation Syndrome (mild to moderate)
Uncommon:	Ovarian Hyperstimulation Syndrome (severe)
General disorders and administration site conditions	
Comune:	Fever
Musculoskeletal and connective tissue disorders	
Common:	Arthralgia
MEN	
Reproductive system and breast disorders	
Common:	Gynecomastia
Skin and subcutaneous tissue disorders	
Common:	Acne
Metabolism and nutrition disorders	
Common:	Abnormal weight gain

Ovarian Hyperstimulation Syndrome (OHSS) from mild to moderate degree is a common effect and shall be considered as an implicit risk of the ovarian stimulation procedure.

The first symptoms are pain in the lower abdomen sometimes in combination with nausea and vomit. In severe cases, an ovarian hyperstimulation syndrome with clear enlargement of ovaries can be

associated with accumulation of fluids in the abdomen or chest and weight gain, as with more serious thromboembolic complications which could occur rarely. Thromboembolic events can occur independently from the hyperstimulation.
A careful medical examination is recommended in these cases. Moreover the treatment with FOSTIMON shall be discontinued and the hCG treatment shall not be given.

The incidence of multiple pregnancies is increased by Fostimon as by other medicines used for ovulation stimulation. The majority of multiple conceptions are twins: during ART procedures multiple pregnancies are related mainly to the number of replaced embryos.

In rare cases the therapy with menotrophin / chorionic gonadotropin was accompanied by events of arterial thromboembolism that could occur also during treatment with Fostimon / hCG.

The frequency of abortion is comparable to that found in patients with other fertility problems. In patients with tubal disease there is the possibility that ectopic pregnancies occur.

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 "https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse".

4.9 Overdose
No effects of overdose due to Fostimon were described; however, an ovarian hyperstimulation syndrome could arise, as described in section 4.4..

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: gonadotropins and other ovulation stimulants: urofollitropin: ATC CODE: G03GA04 – gonadotropins.
Women: FOSTIMON contains urofollitropin, a highly purified Follicle Stimulating Hormone (FSH) obtained from human post-Menopausal Gonadotropin (HMG)
The main effect of a FSH injection is the development and maturation of de Graaf follicles.
Men: FOSTIMON, administered in association with hCG for at least 4 months, stimulates sperm production in men with FSH deficiency.

5.2 Pharmacokinetic properties
After a single i.m. administration of 150 IU of urofollitropin in healthy volunteers, the FSH peak is reached in 10 ± 4 hours. An increase of 4 ± 2 IU/L of FSH with respect to the baseline is obtained. 72 hours after the administration of 150 IU of urofollitropin the serum levels of FSH are significantly higher than the baseline. Elimination half-life is about 30-40 hours.

5.3 Preclinical safety data
Toxicology and tolerability studies in animals revealed no noteworthy effects.
In acute toxicity tests performed on mice and rats doses of Urofollitropin higher than 1500 IU/kg were used, in the subacute toxicity studies in rats and monkeys, doses up to 100 IU/kg /day for 13 weeks were used. In studies of the mutagenesis Urofollitropin showed no mutagenic activity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
The vial contains: lactose.
Each ampoule/pre-filled syringe of 1 ml contains: sodium chloride and water for injection

6.2 Incompatibilities
Chemical incompatibilities with FOSTIMON are not known, but it is recommended not to mix the product with other medicines in the same syringe.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Do not store above 25°C.
Keep the medicine in the outer carton in order to protect from light.

6.5 Nature and contents of container
FOSTIMON is available in the following pack-sizes:

FOSTIMON 75 IU/1 ml powder and solvent for solution for injection:
- 1 vial of 75 IU of powder + 1 ampoule of solvent;
- 1 vial of 75 IU of powder + 1 pre-filled syringe of solvent with 2 needles.
- 5 vials of 75 IU of powder + 5 ampoules of solvent;
- 5 vials of 75 IU of powder + 5 pre-filled syringes of solvent with 2 needles each.
- 10 vials of 75 IU of powder + 10 ampoules of solvent;
- 10 vials of 75 IU of powder + 10 pre-filled syringes of solvent with 2 needles each.

FOSTIMON 150 IU/1 ml powder and solvent for solution for injection:
- 1 vial of 150 IU of powder + 1 ampoule of solvent;
- 1 vial of 150 IU of powder + 1 pre-filled syringe of solvent with 2 needles.
- 5 vials of 150 IU of powder + 5 ampoules of solvent;
- 5 vials of 150 IU of powder + 5 pre-filled syringes of solvent with 2 needles each.
- 10 vials of 150 IU of powder + 10 ampoules of solvent;
- 10 vials of 150 IU of powder + 10 pre-filled syringes of solvent with 2 needles each.

FOSTIMON 225 IU/1 ml powder and solvent for solution for injection:
- 1 vial of 225 IU of powder + 1 pre-filled syringe of solvent with 2 needles.
- 5 vials of 225 IU of powder + 5 pre-filled syringes of solvent with 2 needles each.
- 10 vials of 225 IU of powder + 10 pre-filled syringes of solvent with 2 needles each.

FOSTIMON 300 IU/1 ml powder and solvent for solution for injection:
- 1 vial of 300 IU of powder + 1 pre-filled syringe of solvent with 2 needles.
- 5 vials of 300 IU of powder + 5 pre-filled syringes of solvent with 2 needles each.
- 10 vials of 300 IU of powder + 10 pre-filled syringes of solvent with 2 needles each.

Containers:
Glass type I *vial* with an elastomeric stopper and aluminium seal with plastic flip-off cap.
Glass type I *ampoule*.
Glass type I pre-filled syringe with elastomeric tip cap provided with stopper in elastomeric material and back-stop device.

Each pre-filled syringe is provided with the following needles:
- 21 gauge needle (0.8 mm x 40 mm) with GREEN cap for the reconstitution of the solution and the intramuscular injection;
- 27 gauge needle (0.4 mm x 12 mm) with GREY cap for subcutaneous injection;

Not all pack-sizes may be marketed
.

6.6 Special precautions for disposal
To avoid possible waste of FSH due to adhesion to the wall of the syringe, Fostimon should be administered immediately after reconstitution. In any case, the degree of dispersion that may occur does not have significant effects on the dose required for clinical efficacy.

Directions for the reconstitution of solution

1. Preparation

Each vial is for single use only. The medicinal product must be reconstituted under aseptic conditions, after washing hands thoroughly.
Solvent in ampoule: draw the solvent into the ampoule through a syringe
Solvent in pre-filled syringe: remove the cap from the prefilled syringe, insert the 21 gauge needle (green cap) for the reconstitution of solution.

2. Reconstitution of solution

- Remove the flip-off cap from the powder vial
- Inject the solvent into the vial through the elastomeric stopper
- Swirl the vial slowly to dissolve the powder
- Once the powder is dissolved (which, in general, occurs immediately), slowly draw the solution into the syringe. The solution must be clear and colourless.

3. Administration

If necessary, remove the needle used for the reconstitution and insert the needle suitable for the administration.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

FOSTIMON 75 IU/1 ml powder and solvent for solution for injection:
- 1 vial + 1 ampoule 032921013
- 1 vial + 1 pre-filled syringe 032921076
- 5 vials + 5 ampoules 032921037
- 5 vials + 5 pre-filled syringes 032921088
- 10 vials + 10 ampoules 032921049

10 vials + 10 pre-filled syringes 032921090

FOSTIMON 150 IU/1 ml powder and solvent for solution for injection:
- 1 vial + 1 ampoule 032921025
- 1 vial + 1 pre-filled syringe 032921102
- 5 vials + 5 ampoules 032921052
- 5 vials + 5 pre-filled syringes 032921114
- 10 vials + 10 ampoules 032921064
- 10 vials + 10 pre-filled syringes 032921126

FOSTIMON 225 IU/1 ml powder and solvent for solution for injection:

1 vial + 1 pre-filled syringe 032921138
- 5 vials + 5 pre-filled syringes 032921140
- 10 vials + 10 pre-filled syringes 032921153

FOSTIMON 300 IU/1 ml powder and solvent for solution for injection:
- 1 vial + 1 pre-filled syringe 032921165
- 5 vials + 5 pre-filled syringes 032921177
- 10 vials + 10 pre-filled syringes 032921189

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

FOSTIMON 75 IU/1 ml powder and solvent for solution for injection:
- 1 vial + 1 ampoule 12/2008
- 1 vial + 1 pre-filled syringe 01/2014
- 5 vials + 5 ampoules 12/2008
- 5 vials + 5 pre-filled syringes 01/2014
- 10 vials + 10 ampoules 12/2008
- 10 vials + 10 pre-filled syringes 01/2014

FOSTIMON 150 IU /1 ml powder and solvent for solution for injection:
- 1 vial + 1 ampoule 12/2008
- 1 vial + 1 pre-filled syringe 01/2014
- 5 vials + 5 ampoules 12/2008
- 5 vials + 5 pre-filled syringes 01/2014
- 10 vials + 10 ampoules 12/2008
- 10 vials + 10 pre-filled syringes 01/2014

FOSTIMON 225 IU /1 ml powder and solvent for solution for injection:
- 1 vial + 1 pre-filled syringe 11/2014
- 5 vials + 5 pre-filled syringes 11/2014
- 10 vials + 10 pre-filled syringes 11/2014

FOSTIMON 300 IU /1 ml powder and solvent for solution for injection:
- 1 vial + 1 pre-filled syringe11/2014
- 5 vials + 5 pre-filled syringes 11/2014
- 10 vials + 10 pre-filled syringes 11/2014

10. DATE OF REVISION OF THE TEXT

11/2020

11. CONDITIONS OF PRESCRIPTION AND DISPENSING

Medicinal product subject to medical prescription (RR)

12. PACKAGING AND CLASSIFICATION FOR REFUNDABILITY

- "75 IU / 1ml powder and solvent for solution for injection for intramuscular or subcutaneous use" 1 vial + 1 ampoule - Class A, note 74. Retail price € 21.53
- "75 IU / 1ml powder and solvent for solution for injection for intramuscular or subcutaneous use "10 vials + 10 vials - Class A, note 74. Retail price € 215.34
- " 150 IU / 1ml powder and solvent for solution for injection for intramuscular or subcutaneous use "1 vial + 1 pre-filled syringe with 2 Class A needles, note 74. Retail price € 43.07
- "150 IU / 1ml powder and solvent for solution for injection for intramuscular or subcutaneous use" 5 vials + 5 pre-filled syringes with 10 Class A needles, note 74. Public price € 215.38
- "225 IU / 1ml powder and solvent for solution for injection for intramuscular or subcutaneous use" 1 vial + 1 pre-filled syringe with 2 needles Class A, note 74. Retail price € 64.60
- "225 IU / 1ml dust and solvent for solution for injection for intramuscular or subcutaneous use "5 vials + 5 pre-filled syringes with 10 needles Class A, note 74. Retail price € 323.00
- " 300 IU / 1ml powder and solvent for solution for injection for intramuscular or subcutaneous use "1 vial + 1 pre-filled syringe with 2 Class A needles, note 74. Retail price € 86.13
- " 300 IU / 1ml powder and solvent for solution for injection for intramuscular or subcutaneous use "5 vials + 5 pre-filled syringes with 10 needles Class A, note 74. Retail price € 430.67

References

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4. Andersen CY et al. FSH-induced resumption of meiosis in mouse oocytes: effect of different isoforms. Mol Hum Reprod 1999;5(8):726-31.
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7. Wide L et al. Serum half-life of pituitary gonadotropins is decreased by sulfonation and increased by sialylation in women. J Clin Endocrin Metab 2009;94(3):958-64.
8. Andersen CY et al. FSH isoform composition of commercial gonadotrophin preparations: a neglected aspect? Reprod Biomed Online 2004;9(2):231-6.

Code 75000001233

Meriofert® Italian price and refundability

Powder and solvent for solution for subcutaneous or intramuscular injection.

- 75 IU/1ml: 1 glass vial - Retail price € 26.57; 5 glass vials - Retail price € 132.87.
- 150 IU/1ml: 1 glass vial - Retail price € 53.14; 5 glass vials - Retail price € 265.72.

Class A, Note 74, Repeatable medical prescription (RR).

Fostimon® Italian price and refundability

Powder and solvent for solution for subcutaneous or intramuscular injection.

- 75 IU/1ml: 1 vial + 1 ampoule - Retail price € 21.53; 10 vials + 10 ampoules - Retail price € 215.34.
- 150 IU/1ml: 1 vial + 1 pre-filled syringe + 2 needles - Retail price € 43.07; 5 vials + 5 pre-filled syringes +10 needles - Retail price € 215.38.
- 225 IU/1ml: 1 vial + 1 pre-filled syringe + 2 needles - Retail price € 64.60; 5 vials + 5 pre-filled syringes + 10 needles - Retail price € 323.00.
- 300 IU/1ml: 1 vial + 1 pre-filled syringe + 2 needles - Retail price € 86.13; 5 vials + 5 pre-filled syringes + 10 needles - Retail price € 430.67.

Class A, Note 74, Repeatable medical prescription (RR).

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