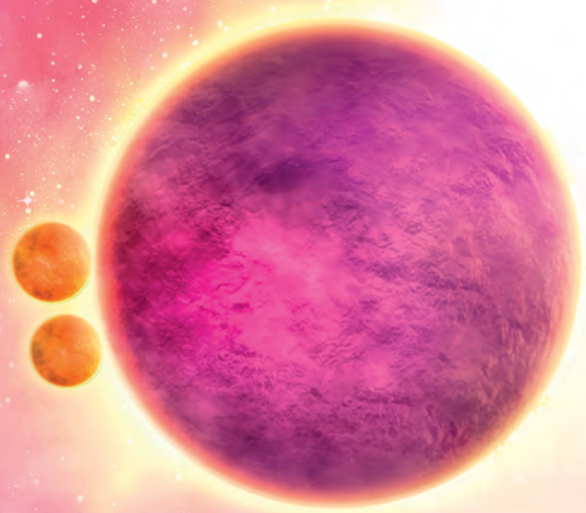
Fostimon®

Highly Purified hFSH

Origins of life

Following nature's model.



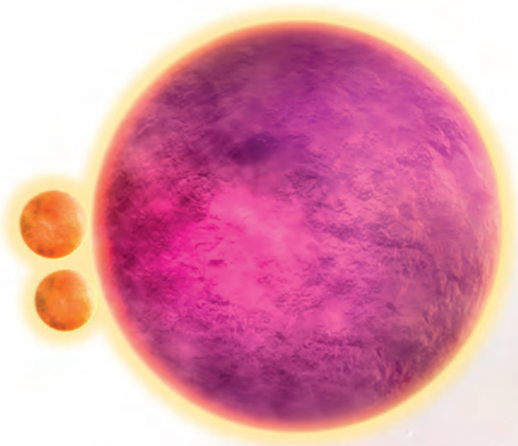
Prescribing information on page 19.

IBSA

Caring Innovation

* See table of Fostimon® Clinical Studies on pages 16, 17

Fostimon® | Highly Purified hFSH



Introducing an innately human essence of the highest quality in ART programs.

EXCLUSIVE

Recognising the crucial importance of glycosylation in FSH, IBSA developed and patented a non-aggressive purification system to obtain a full range of FSH isoforms at the highest purity[1,2].

NATURE-INSPIRED

IBSA's highly purified FSH is rich in highly glycosylated (acidic) isoforms[2]. In a natural cycle, these isoforms predominate in the early follicular phase and are essential for effective recruitment and optimal maturation of oocytes[3-5].

RELIABLE

Over fifteen years of clinical experience and randomised, controlled clinical studies confirm that **Fostimon®** is an effective and reliable alternative to existing FSH preparations.*

IBSA

Follicle-stimulating hormone (FSH)

Follicle-stimulating hormone (FSH) is a major player in folliculogenesis and oocyte maturation. FSH binds to its ovarian receptor to sustain oocyte maturation up to the release of a single mature oocyte.
Other FSH actions include stimulation of steroidogenesis resulting in estrogen production, granulosa cell proliferation, induction of luteinising hormone receptors (LH-R) and its own receptors (FSH-R)[6].

FSH can be used as therapeutic support to induce the maturation of single or multiple follicles as part of assisted reproduction programs.
(Fostimon® Smpc)

FSH structure

FSH is a complex glycoprotein made of a proteic part and a glycidic part (carbohydrate), which is about 30% of its molecular mass. The proteic part is composed by two non-identical α and β subunits: β accounts for the specific biological properties of FSH. Each proteic subunit has two possible N-linked glycosylation sites (Figure 1) for the carbohydrate. Consequently, FSH exists as a family of **isohormones or isoforms**, which differ in their ionic charge due to variance in their carbohydrate structure, including variations in the total number of charged terminal sialic acid and, to a lesser extent, the sulphate residues[7].

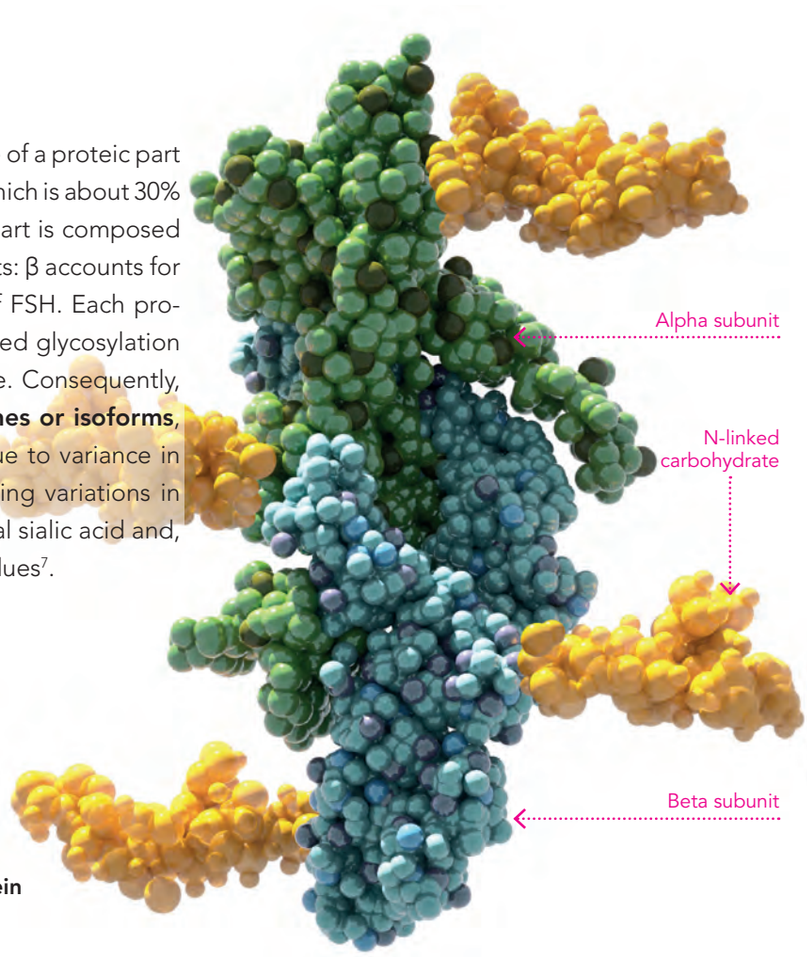


Figure 1. FSH is a complex glycoprotein
(Adapted from textual data)[7]

HIGHLIGHT

FSH is a complex glycoprotein, existing as a family of isoforms, which differ in their ionic charge due to great variance in their carbohydrate structure[7].

FSH isoform (FSH)

The carbohydrates characterise the different isoforms (Figure 2): they are actually made of a sequence of sugars; in particular, there is a 'core' of mannose with 1 to 4 branches or antennae made of N-acetyl glucosamine, galactose and sialic acid.

The pituitary gland releases **highly glycosylated and low glycosylated (acidic or less acidic) isoforms depending on the sialic content**, with different degrees of complexity of the carbohydrate branching pattern. Nature's several combinations of carbohydrate structures thus occur, playing a key role in determining the different functional properties of FSH. The carbohydrate structure characterises these different FSH **isoforms** and affects and modulates the affinity of FSH for its receptor[8].

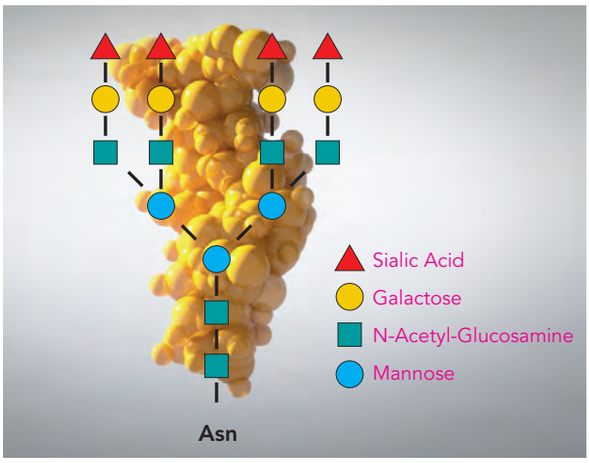


Figure 2. Schematic representation of the carbohydrate chains of the FSH molecule (Adapted from textual data)[8]

The higher the number of branches and of sialic acid molecules, the higher the acidity of the molecule (Figure 3). Actually, the anterior pituitary gland produces a mix of differently glycosylated/sialylated isoforms, covering a wide range of acidity.

Depending on their sialic content, the potential of these naturally occurring isoforms to evoke a specific effect at the target cell level may differ. Studies in a variety of species and in humans have clearly demonstrated this heterogeneity of FSH[3].

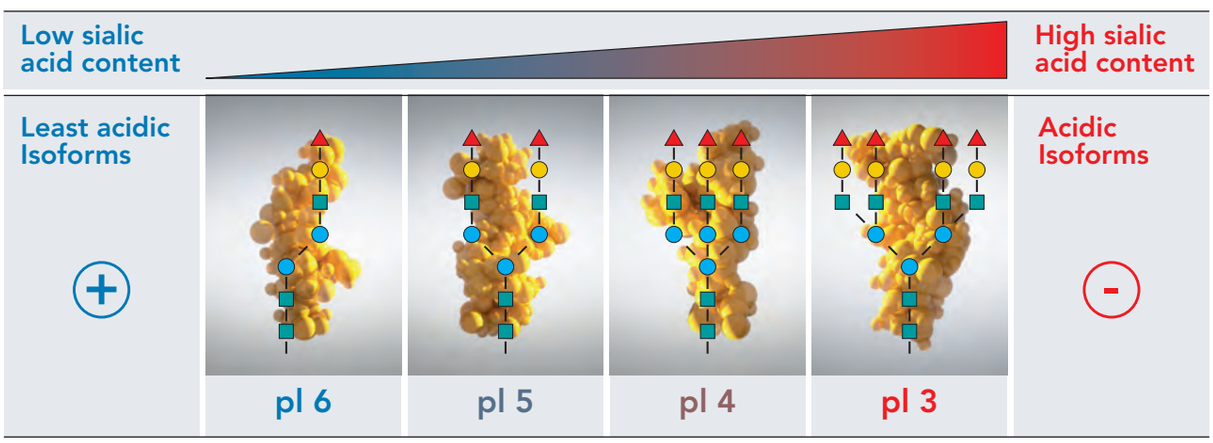


Figure 3. Schematic representation of human pituitary range of FSH isoforms according to the isoelectric point (pI) (Adapted from textual data)[3]

In IBSA's human Highly Purified FSH (hFSH), specific analyses have shown a predominance of highly sialylated, highly branched carbohydrates as compared to recombinant FSH (rFSH) expressed in rodent cell lines.

The antennary structure is crucial for many *in vivo* biological activities of hFSH, regulating folding, secretion, immunogenicity, and plasma half-life, as well as modulating some biological behaviors[2].

Half-life of FSH isoforms

The glycosylation and specifically the content at sialic acid of FSH isoforms directly correlate with their half-life. The more glycosylated and sialylated isoforms have shown a significantly longer half-life *in vivo*[9,10], due to a reduced first pass hepatic catabolism: the sialic acid 'cap' prevents hepatic degradation of the carbohydrate moiety, thus conferring higher bio-availability to the FSH molecule and allowing higher circulating levels (Figure 4).

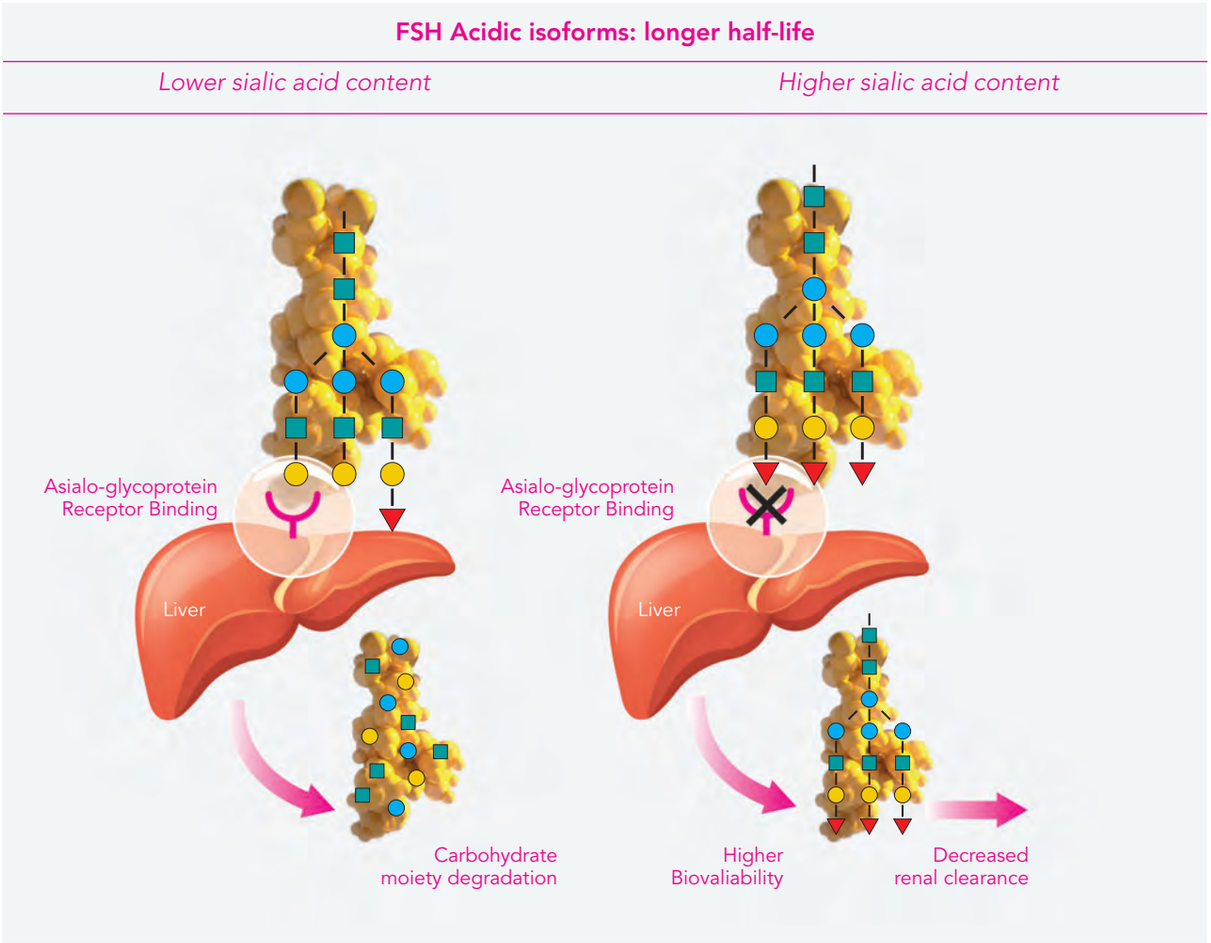


Figure 1. Schematisation of the metabolic pathway of non-acidic and acidic FSH molecules
(Adapted from textual data)[9,10]

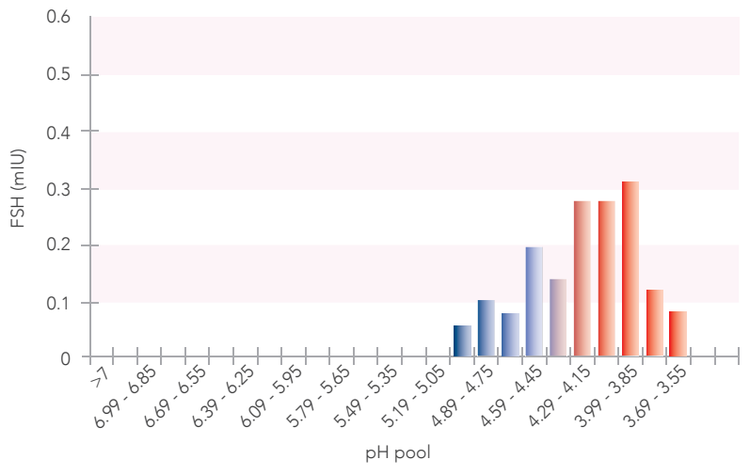
HIGHLIGHT

The carbohydrate chains play a key role in determining the different functional properties of the FSH molecule, including metabolic clearance (half-life) and are important for determining receptor-binding affinity and receptor activation[9,10].

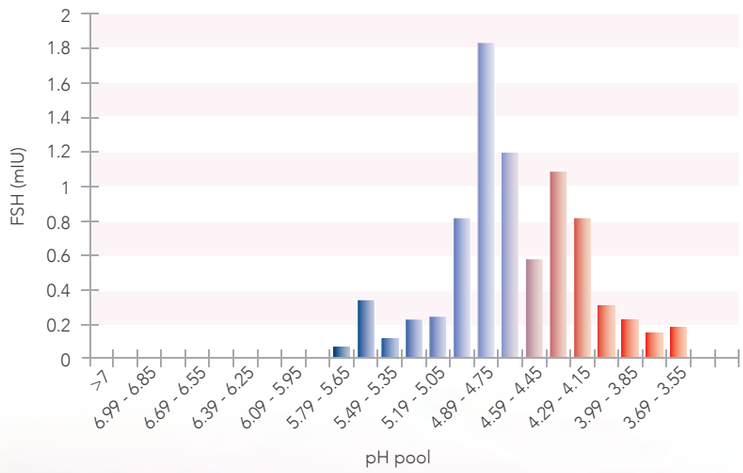
The changing FSH isoform profile during the menstrual cycle

Highly glycosylated, acidic isoforms are predominantly released in the early follicular phase and drop approaching ovulation to progressively rise back during the luteal-follicular transition. On the other hand, **less acidic isoforms are more common as ovulation approaches**[4] (Figure 5).

Early-mid follicular phase



Midcycle



Charged distribution of FSH by chromato-focusing of serum samples taken from one woman at different stages of her menstrual cycle[8].

Figure 5. Isoform distribution of FSH at different stages of the menstrual cycle (Adapted from Anobile 1998)[4]

More acidic isoforms are required for effective recruitment and optimal maturation of oocytes, while the less acidic isoforms are physiologically relevant in the periovulatory period and are significantly more effective in stimulating the synthesis and secretion of estrogens[4,5].

It is the increase in estrogen levels in the preovulatory phase of the menstrual cycle that drives the shift from the secretion of acidic FSH isoforms to isoforms with relatively low sialic acid content (Figure 6). It has been shown that during the mid-cycle phase of the normal cycles there was a shift of FSH isoforms (as measured by immunoassay) to the basic pH range. In contrast, in the mid- to late luteal phase there was an increase in FSH isoforms in the acidic pH range. Therefore, it appears that estrogenic stimulation causes preferential secretion of less acidic isoforms with increased biological activity[11,12].

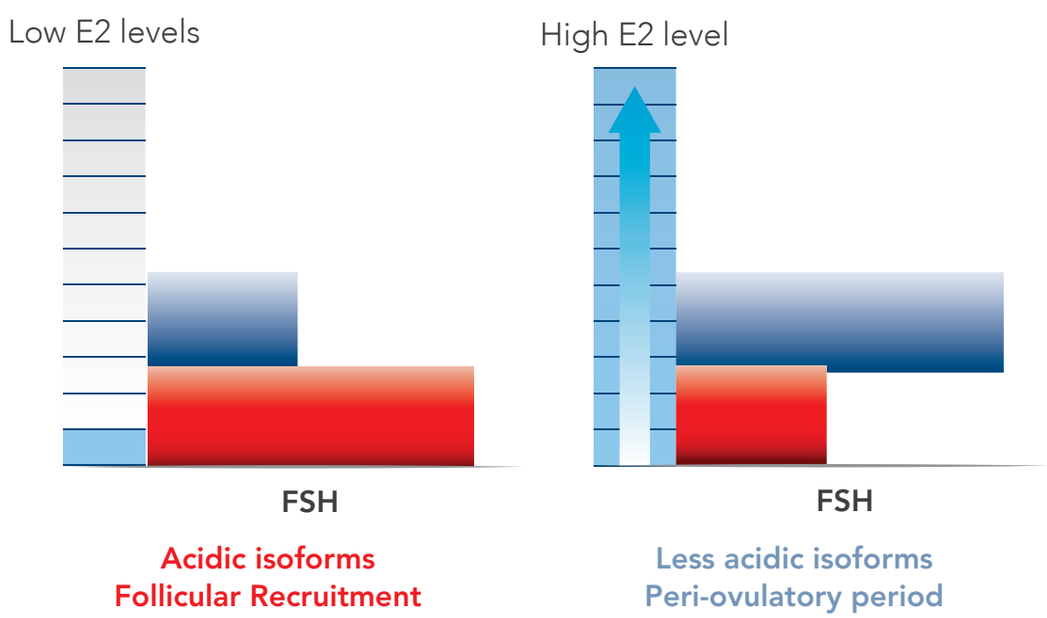


Figure 6. Schematic representation of estrogen levels during the menstrual cycle and natural pattern of release of FSH isoforms (Adapted from textual data)[11]

The increase in estrogen levels drives the shift from the more acidic isoforms to the less acidic isoforms as ovulation approaches[11].

Role of different FSH isoforms

Proper follicular development probably depends on specific and timely exposure to particular FSH isoform mixtures[5].

Acidic isoforms

When sustained gonadal stimulation is essential, such as during the early follicular phases of menstrual cycles - when follicular recruitment and growth of the follicle are occurring - a more acidic mix of FSH isoforms prevails in the circulation. It has been shown that acidic isoform mixtures actually **facilitate ovarian follicular maturation**[11,13]. Acidic isoforms of FSH, compared to less acidic ones, induce **greater production of inhibin,** which exerts a negative feedback on the pituitary, thereby producing less FSH and and allowing for a fine-tuning of the follicular maturation and the recruitment of fewer but better selected follicles[3].

Less acidic isoforms

During the periovulatory period, a significant increase in secretion of less acidic isoforms has consistently been observed. This means that, at times **when an acute and potent signal is essential to accelerate the growth of the pre-ovulatory follicle, increased proportions of less acidic FSH isoforms are present** in the circulation[11,13].

It has been demonstrated that FSH isoforms with pI >5.0 induced resumption of meiosis more efficiently than acidic isoforms. Studies in animal models have shown that the low concentrations of less acidic isoforms produce the most rapid growth of follicles[7], and that follicles exposed to the low levels of less-acidic isoforms result in rapid development of two-cell embryos in 80% of the oocytes, after subsequent *in vitro* maturation[5].

Thus, resumption of meiosis seems to be synergistic with final pre-ovulatory follicle maturation.

SUMMARY[3,5,7,11-13]

Natural pattern of release of FSH isoforms during the menstrual cycle

FSH isoforms	Acidic isoforms	Less acidic isoforms
Acidic isoforms during follicular recruitment	Sustained stimulation of follicles	Acute & potent stimulation
Less acidic isoforms before ovulation	Longer half-life	Massive estrogen production
Estrogen level-driven shift	Growth and maturation	Resumption of meiosis

A nature-inspired model

The divergent effects of acidic and less acidic isoforms may be **critical for a more precise regulation of the ovarian response to the gonadotropic stimulus *in vivo*,** allowing for an optimal follicular development[3,5].

Consequently a Nature-inspired model of COH, foreseeing the use of a wide range of FSH isoforms, may also be beneficial for:

- Oocyte quality
- Endometrial coordination

Oocyte quality

There is a strong link between follicular growth and oocyte development: in the animal model, it was shown that the role of FSH in the acquisition of the oocyte developmental competence is primarily associated with its effects on follicular growth.

Indeed, the oocyte quality depends on which and how much genetic information the oocyte may accumulate before germinal vesicles breakdown (Figure 7). **The optimal oocyte quality requires perfect follicular timing and differentiation[14,15].**

Oocyte's transcription silencing
Schematic representation of genetic activities (transcription in blue dotted line) in the oocyte during follicular differentiation.

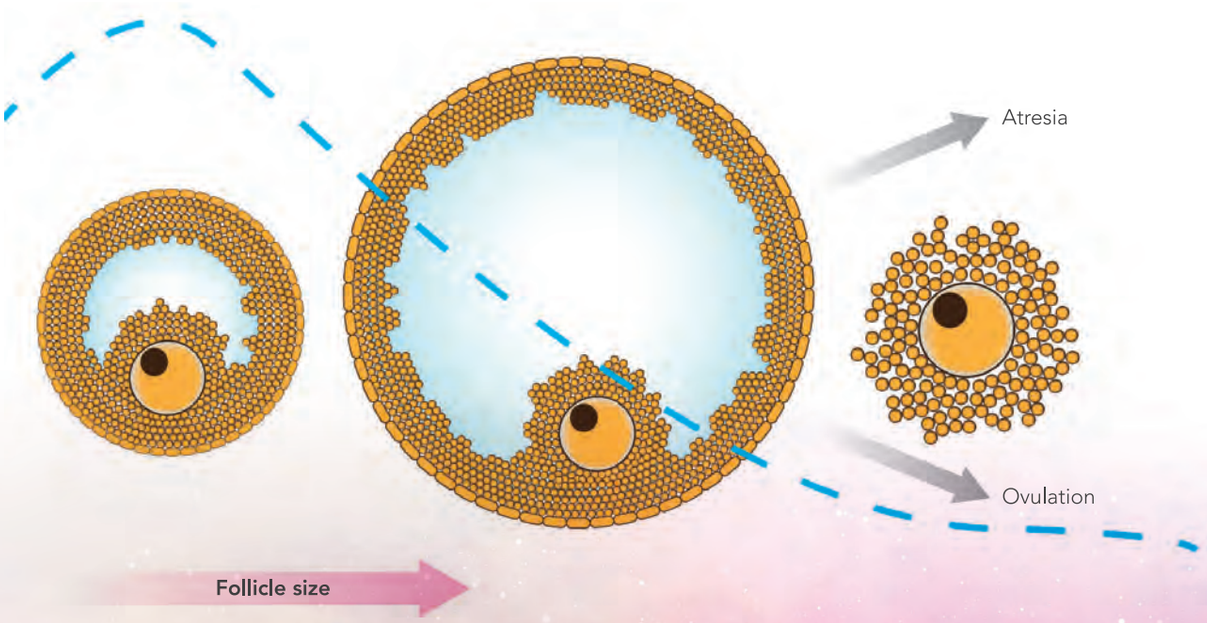


Figure 7. (Adapted from Sirard 2012)[14]

The timely exposure to mixtures of different FSH isoforms mixtures has an impact on follicular development:

• It has been shown that follicular development results in **oocytes with a superior developmental competence when the action of less acidic isoforms is accompanied by the presence of more acidic isoforms**[5]**.**

• On the other hand, findings have shown that continuing exposure to less acidic isoforms only, without the buffering effect of other isoforms, may be detrimental for embryo development[5,16,17].

• Exposure to relative high concentrations of less acidic isoforms *in vitro* may result in disorganized follicular development that causes inability to sustain proper oocyte maturation, with a detrimental effect on embryo development[5,16].

Endometrial coordination

Less acidic isoforms exhibit a lower dissociation constant to their cognate receptor, which may explain the greater capacity to stimulate estrogen production by granulosa cells[3].

The majority of implantation failures after conventional controlled ovarian stimulation (COS) are due to endometrial impairment from COS itself. One possible mechanism of impairment is the advancement of the receptive phase, which results in embryo–endometrium asynchrony[18,19]**.**

The impact of ovarian stimulation on endometrial receptivity is critical. Abnormal concentrations of estrogens and progesterone secondary to ovarian stimulation might affect the endometrial morphology and thereby the endometrial receptivity[19].

An early and massive production of estrogens (E) during the early follicular phase may contribute to changes in the endometrium leading to this embryo-endometrial asynchrony[18,19].
In the natural model, the gradual E increase ensured by acidic FSH isoforms might allow for adeguate coordination of the endometrial preparation, thus possibly favouring implantation.

SUMMARY[3,5,14-19]

Oocyte/ embryo quality	E elevation in follicular phase	Endometrial coordination
Mix of isoforms are needed for good developmental competence	Early E elevation due to eccessive FSH	Early rise of E determines asynchrony of embryo-endometrium development

Less acidic FSH isoforms induce even more E.

Acidic FSH isoforms in the follicular phase allow for more gradual E increase

Fostimon® purification process: the IBSA innovation

There are two main variables that influence the glycosylation content in the final FSH products[20]:

- the type of raw material to be purified
- the purification process

Recombinant FSH

In recombinant FSH (recFSH), the level of glycosylation of the final product is influenced by the nature of the starting material to purify.

The FSH proteic α and β subunits are produced within the cell ribosomes and their aminoacidic sequence is genetically encoded; this means that inserting the gene of the human FSH in laboratory cell lines, such as the Chinese hamster ovary (CHO) cells, the α and β subunits can be entirely replicated[20].

On the other hand, **the glycidic part of the glycoprotein, the carbohydrate chains, are produced and attached to the proteins in the Golgi apparatus and this step totally depends on the cell enzymatic pool[21].** (Figure 8)

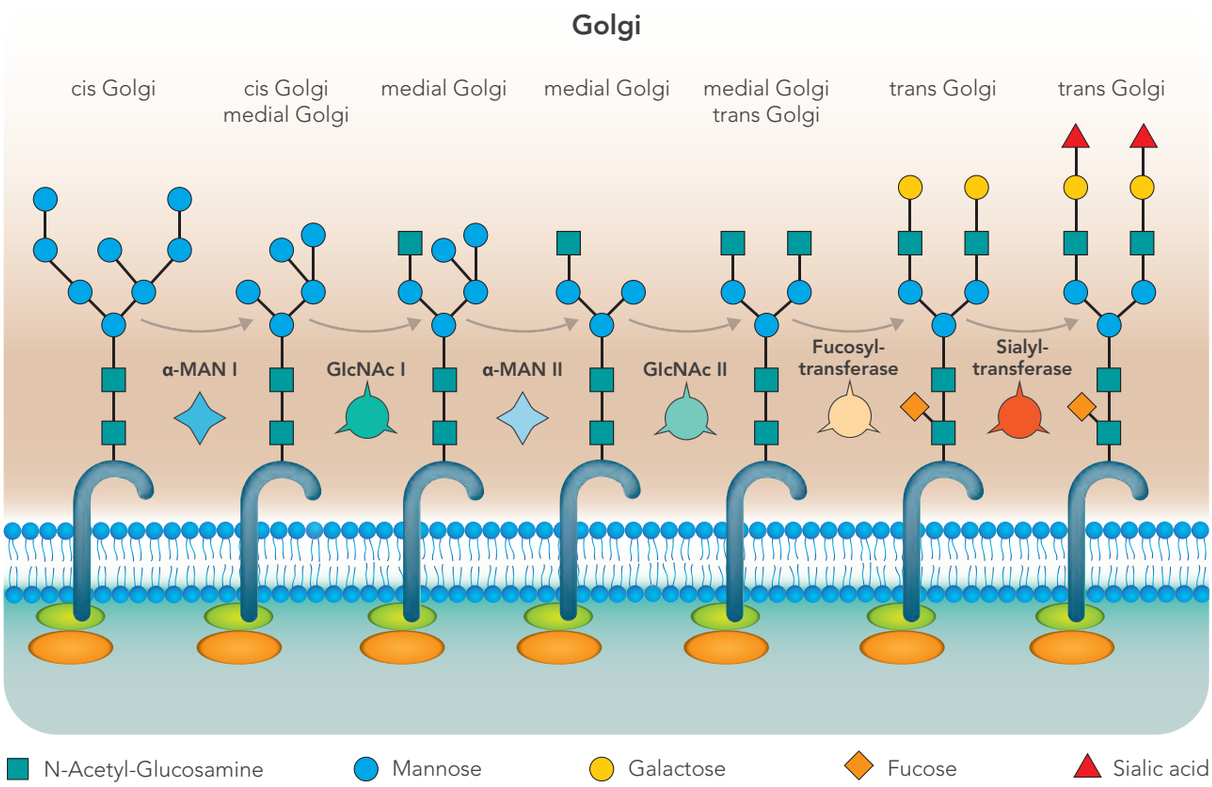
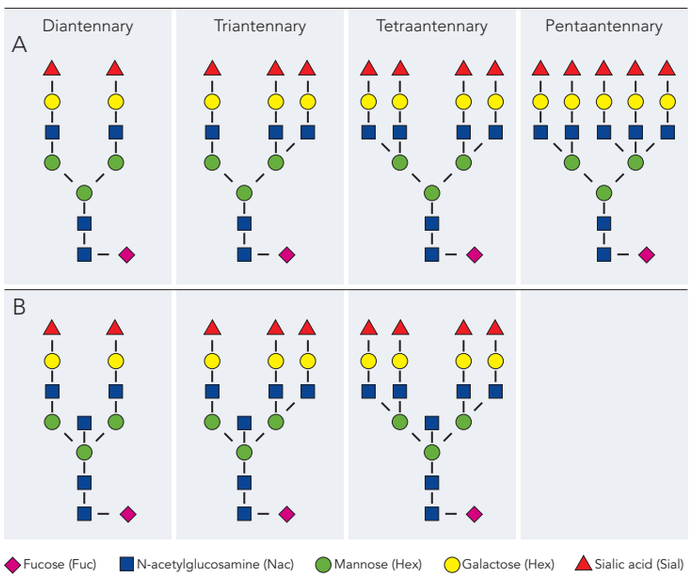


Figure 8. The proteic subunits α and β are glycosylated by the cellular enzymes
(Adapted from textual data)[21]

The resulting glycosylation process is species-specific, entirely depending on the type of enzymatic pool of the producing cells. Rodent cells, which are typically used to produce recombinant FSH, have a different enzymatic machinery compared to human cells.

The rec-FSH produced by CHO cells therefore exhibits less branched carbohydrate structures than pituitary and extracted FSH[2].
In other words, rec-FSH has the same proteic backbone of the human-derived FSH, but is poorer in carbohydrate chains antennarity. (Figure 9).



A) Complete antennary structures of N-glycans in hFSH α- and β-subunits.

B) Bisecting antennary structures, which may derive from the lack of one Hex in the complete structures.

Figure 9. (Adapted from Lombardi 2013)[2]

Due to its content in low-glycosylated forms, rec-FSH isoform distribution is in the range of the less acidic isoforms[2].

Extractive FSH

In the case of extractive FSH, the final glycosylation range is mainly affected by the purification process.

There is a specific pattern of release of different FSH isoforms during a woman's reproductive life. It is well known that with aging the ovary produces increasing amounts of FSH, with increasing mean levels of glycosylation. At the time of menopause, almost all circulating FSH is highly glycosylated and more acidic[2,12].

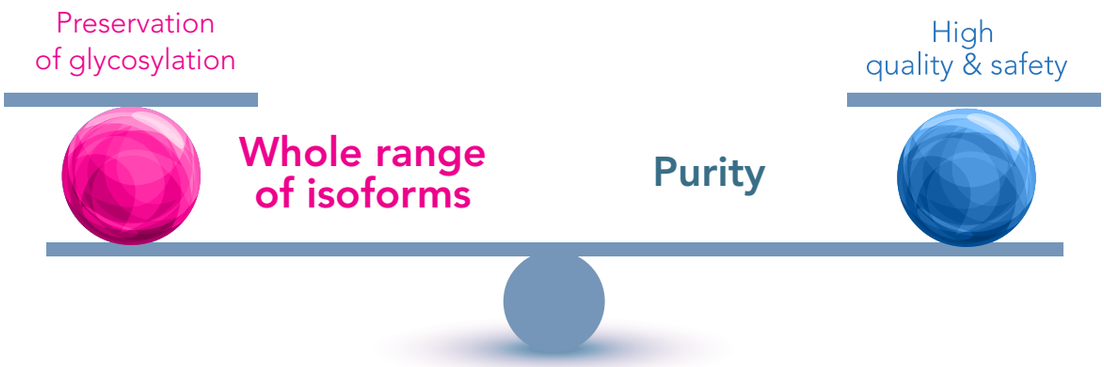
IBSA's extractive FSH is produced exclusively by human cells and extracted from menopausal women's urines, and is therefore rich in glycosylated acidic FSH isoforms[2,34].

For many years, the development of gonadotropin drug products was driven by the need of increasing purity, whereas little attention was paid to the level of glycosylation of the molecules. While purity is not an issue anymore, the ordinary urine purification process to obtain extractive FSH is complex and may cause the detachment of the sugars.

IBSA's purification process

Recognising the critical importance of sugars in the FSH molecules, IBSA developed and patented a new purification process that preserves glycosylation[1].

The challenge is to maintain high purity and quality, while preserving glycosylation in adequate balance.



IBSA's approach has been to develop a new, patented purification process using state-of-the-art technology and know-how.

Under the same global quality assurance system, the all-in-house workflow includes:

Urine collection

Early purification

Final purification

HIGHLIGHT

IBSA's approach is a new, patented purification process that leverages on the best-advanced technologies and know-how. IBSA's innovative purification process preserves the whole range of natural FSH isoforms, while guaranteeing the maximal level of purity[2].

Ibsa's purification protocol is a non-aggressive two-step process, based on selective precipitation and solubilisation steps to eliminate contaminants, while preserving the structure of gonadotropins.

Step 1: Early purification

The initial purification is aimed at reducing the load of proteins, by exploiting the chemical properties of the molecules. It consists of a non-aggressive process, based on selective precipitation and solubilisation steps to eliminate other components of the solution, preserving the inner structure of FSH and its isoforms (figure 10). This avoids the use of further aggressive chemicals to reach the targeted purity, preventing the loss of sugars, which are critical to final product quality.

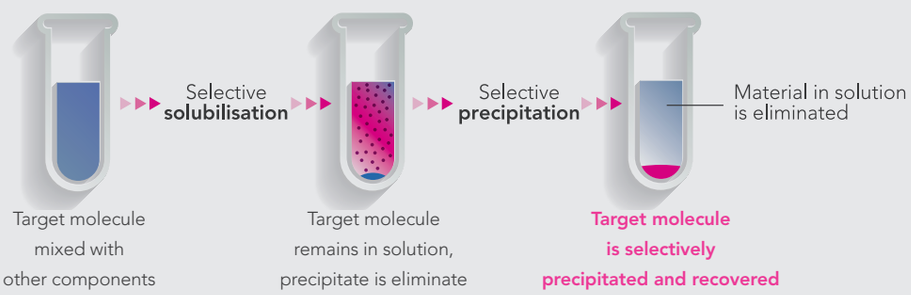


Figure 10.

Step 2: Final purification

The final purification steps include a series of cromatographies that allow for recovery of the whole range of FSH isoforms, excluding impurities.

The most important **high affinity chromatography** is based on a **blue sepharose resin, an innovation in the approved patent** that enables high selectivity in fractionating the different protein species and **extended recovery of all FSH species (including very acidic isoforms), thereby ensuring a high purification yield.**

FSH isoform range

By implementing its patented purification process that preserves the sugar moieties, Fostimon® appears to contain more highly glycosylated FSH molecules (more acidic isoforms) than recombinant FSH products[2].

The oligosaccharide composition of commercial follicle stimulating hormone preparations has been evaluated[2]. Technological improvements in analytical techniques and bioinformatics enabled characterising both both the α- and β-subunits of urinary human FSH (Fostimon®) in comparison with recombinant hFSH (recFSH)[2].

Isoelectrofocusing (IEF) analysis was performed, in order to compare hFSH of different origin. Differences in the net charge distribution were observed, as illustrated in Figure 11. Differences in the band distribution can be seen. Fostimon® showed bands in the more acidic region, whereas for the recFSH forms the bands were shifted toward the more basic region. These results demonstrate the prevalence in Fostimon® of more acidic isoforms, which correspond to species containing more sialylated and branched carbohydrate moieties. In contrast, the less acidic isoforms observed for recombinant FSH correspond to a lower content of sialic acid and a prevalence of diantennary species[2].

Lanes 1, 3, 5, 7:
pI marker (Serva).

Lane 2:
hFSH (Fostimon®, IBSA, Switzerland).

Lane 4:
recFSH (Gonal-f, Merck Serono, Switzerland).

Lane 6:
recFSH (Puregon, Organon, the Netherlands).

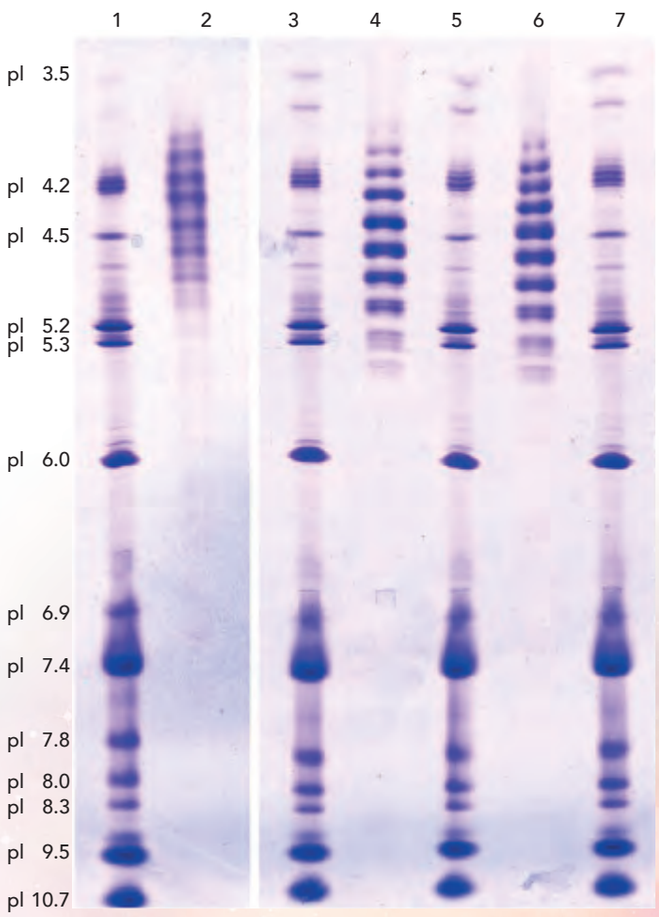


Figure 11. IEF separation of recombinant hFSH and urinary hFSH (Fostimon®) (Adapted from Lombardi 2013)[2]

The molecular species contained in Fostimon® were fully characterised, accurately recording the number of antennae, the composition and completeness of the carbohydrate moieties present in the FSH active compound. **All the results showed that Fostimon® contains a more sialylated, more branched distribution, compared to the commercially available hFSH from recombinant origin.**

These analyses prove that the protocol specifically designed to extract Fostimon® from human urine as a highly purified, pharmaceutical grade product preserves the glycosylation status of the molecule at every step and minimises the possible degradation of the oligosaccharide moieties[2].

The status of carbohydrate residues is essential for the *in vivo* biological activity of the gonadotrophins, because they regulate folding, secretion, and immunogenicity. Furthermore, they are essential for the plasma half-life of the glycoprotein hormones and for modulating some of the other biological behaviours of the hormone[2].

HIGHLIGHT

The differences in the glycosylation pattern of Fostimon® compared to other marketed products whose FSH is obtained from recombinant technologies are also likely to be reflected in different biological properties[2].

The quality of the final product

First author and year of publication	Patients number	Objectives	Conclusions
Selman, 2002[22]	267	To determine the **effects of ovarian stimulation with highly purified urofollitropin on oocyte and embryo quality**, in comparison with recombinant FSH.	Highly purified urinary FSH is as effective, efficient, and safe for clinical use as recombinant FSH.
Mohamed, 2006[23]	257	To determine which FSH, recombinant or urinary, works better in older women (>39 y).	Urinary **FSH performed better in older women than recombinant FSH** when associated with the long protocol.
Pacchiarotti, 2007[24]	119	To evaluate the efficacy of using both urinary and recombinant FSH in a combined protocol for ovarian stimulation in an IVF treatment program.	This study shows that **using a combination of both urinary and recombinant FSH** for ovarian stimulation improves oocyte maturity and embryo cleavage, and increases pregnancy and implantation rates compared to rec FSH alone.
Baker, 2009[25]	152	To compare the efficacy of highly purified human urinary follicle stimulating hormone (HP-hFSH) versus human recombinant follitropin-alpha (rFSH) in volunteers undergoing controlled ovarian stimulation for IVF.	There were **no statistically significant differences in mean oocyte number, clinical pregnancy rate, or live birth rate between HP-hFSH versus rFSH**.
Abate, 2009[26]	401	To evaluate the efficacy on oocyte and embryo quality in *in vitro* fertilisation/ intracytoplasmic sperm injection cycles, comparing human follicle stimulating hormone (hFSH) and recombinant FSH (rFSH).	Fertilisation, cleavage and implantation rates, pregnancy and abortion rates were similar in both groups. In our study, we demonstrated that **hFSH and rFSH products are equivalent in terms of clinical efficacy**. However a significantly higher nr of oocytes was retrieved and the total duration of stimulation and total IU used were significantly lower in Fostimon® group.
Selman, 2010[27]	188	To evaluate the impact of follicle-stimulating hormone (FSH) with different glycosylation patterns on oocyte quality and clinical outcomes in an *in vitro* fertilization (IVF) treatment program.	**The glycosylation patterns of the two types of FSH implemented for ovarian stimulation have different impacts on oocyte quality and clinical outcome. A sequential combined protocol using both acidic and less acidic FSH for ovarian stimulation improves oocyte maturity and embryo cleavage, and increases pregnancy and implantation rates.**
Aboulghar, 2010[28]	84	To compare highly purified urinary FSH with recombinant FSH in IVF/ ICSI cycles for patients with PCOS.	There was no significant difference between the mean total dose of FSH used, duration of stimulation, number of retrieved oocytes, number of mature oocytes, number of embryos transferred, or the ongoing pregnancy rate between the two groups. However, **there were significantly more fertilized oocytes, a higher fertilization rate, more top-quality embryos, and more cryopreserved embryos in the urinary FSH group**.

First author and year of publication	Patients number	Objectives	Conclusions
Murber, 2011[29]	70 cycles	To verify the impact of HP-FSH in comparison with rFSH on oocyte-, embryo quality and embryo development in IVF-ET+ICSI cycles.	There were no significant differences in clinical pregnancy and in live birth rates. Oocytes obtained with HP-FSH stimulation showed higher fertilisability, whereas pregnancy and live birth rates did not differ between the groups. However, **patients treated with HP-FSH may benefit from the higher rate of embryos capable for cryopreservation, suggesting that cumulative pregnancy rates might be higher in this group.**
Kemeter, 2013[30]	1051 cycles	**Differences in the mode of action between recombinant FSH (rFSH) and urinary derived FSH (uFSH) have been reported in cycles down-regulated by agonists. The aim of this study was to determine if these differences also exist in cycles down-regulated by antagonists.**	The results of this study seem to support the concept that uFSH produces fewer oocytes than rec-FSH, but of better quality. Preclinical studies have shown that different FSH isoforms with different elimination kinetics in the two gonadotropin preparations could be responsible for the different effects.
Selman, 2013[31]	197	To evaluate the effect of a combined stimulation protocol of human FSH and recombinant FSH, simultaneously administered, on oocyte and embryo quality and clinical outcome.	**The results show that the combination of human and recombinant FSH for ovarian stimulation may produce a positive effect on follicular development as it improve oocyte quality, embryo development, and ultimately clinical outcome.**
Gurgan, 2014[32]	90	To find proposed biomarkers that might be used to predict and screen for oocyte quality, with the implication that this could also predict embryo quality.	Although there was a positive tendency in favor of the sequential treatment, there was no significant difference in pregnancy rates, even taking frozen embryos into consideration. **The cumulus cell transcriptome varied considerably between the treatments, although with no clear significance**.
Colacurci, 2014[33]	230	To investigate if a stimulation protocol using urinary-FSH during the early follicular phase and then shifting toward recombinant-FSH may improve oocyte quality and pregnancy rate in 35–40 years old patients in IVF program.	A sequential protocol using urinary- FSH in the early days of stimulation and subsequently recombinant-FSH may improve the IVF outcome in patients of advanced reproductive age. **The sequential protocol can be used as a specific procedure in those women undergoing IVF that need an improved oocytes quality**.

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34 Fostimon SmPC

Date of last revision: January 12, 2018

Summary of product characteristics

1. NAME OF THE MEDICINAL PRODUCT

Fostimon® PFS 75 IU powder and solvent for solution for injection
Fostimon® PFS 150 IU powder and solvent for solution for injection
Fostimon® PFS 225 IU, powder and solvent for solution for injection
Fostimon® PFS 300 IU, powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 75 IU of urofollitropin (follicle-stimulating hormone FSH): 1 ml of reconstituted solution contains either 75 IU, 150 IU, 225 IU, 300 IU, 375 IU or 450 IU of urofollitropin when respectively 1, 2, 3, 4, 5 or 6 vials of product are reconstituted in 1 ml of solvent.
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 of product are reconstituted in 1 ml of solvent.
One vial contains 225 IU of urofollitropin (follicle-stimulating hormone FSH): 1 ml of reconstituted solution contains either 225 IU or 450 IU of urofollitropin when respectively 1 or 2 vials are reconstituted in 1 ml of solvent.
One vial contains 300 IU of urofollitropin (follicle-stimulating hormone FSH): 1 ml of reconstituted solution contains 300 IU of urofollitropin.

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® PFS 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® PFS is to develop a single mature de Graaf follicle from which the ovum will be released after the administration of human chorionic gonadotropins (hCG).
  Fostimon® PFS 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® PFS is then discontinued and ovulation can be induced by administering human chorionic gonadotropins (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® PFS 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 gonadotropins releasing hormone agonist (GnRH agonist).
  In a commonly used protocol the administration of Fostimon® PFS 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® PFS injection, to induce final follicular maturation.
  Oocyte retrieval is performed 34-35 hours later.

Method of administration

Fostimon® PFS is intended for 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® PFS should be slowly administered subcutaneously. The subcutaneous injection site should be alternated to prevent lipo-atrophy. Any unused solution should be discarded.
Subcutaneous injections can be self-administered by the patient, provided the physician's instructions and recommendations are strictly followed.

4.3 Contraindications

- Hypersensitivity to 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® PFS 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® PFS 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® PFS 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® PFS 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® PFS 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 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 gonadotropins. In these women, the benefits of gonadotropins 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® PFS in humans. Although there is no clinical experience, it is expected that the concomitant use of Fostimon® PFS and clomifene citrate may enhance the follicular response.

4.6 Fertility, Pregnancy and Lactation

Pregnancy
Fostimon® PFS 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® PFS 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® PFS 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 from 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 thromboembolism has 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 systems.

4.9 Overdose
No data on acute toxicity of FSH in humans is available, but the acute toxicity of urinary gonadotropins 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® PFS 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® PFS, Cmax is 5.74 ± 0.95 IU/l, and Tmax is 21.33 ± 9.18 hours. AUC0-∞ 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-foetal mortality in the rat and in the rabbit.
Fostimon® PFS 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 pre-filled syringe of solvent in the outer carton, in order to protect from light.

6.5 Nature and contents of container
Powder in a vial (siliconized type I glass), with a stopper (bromobutyl rubber), with a seal (aluminium) and a flip-off cap (plastic) + 1 ml of solvent in a prefilled syringe* (type I glass with silicone), fitted with a backstop device, with a plunger stopper (siliconized chlorobutyl) closed by a tip cap (isopropene-bromobutyl) + 1 needle for the reconstitution and 1 needle for the subcutaneous injection. These 4 elements are packed in a blister (PVC); pack size of 1, 5 and 10 sets**.
*Fostimon® 75-150 IU is also available with the solvent in ampoule.
**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® PFS 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® PFS powder
- one prefilled syringe with solvent
- one needle for preparing the injection
- a fine bore needle for subcutaneous injection

Both intramuscular and subcutaneous routes of administration are possible. In case the intramuscular route is chosen, appropriate intramuscular needles (not provided) will be necessary.

Reconstitution of the solution for injection using 1 vial of powder
Prepare the solution for injection:
1. Remove the cap from the prefilled syringe, attach the reconstitution needle (long needle) to the syringe.
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, remove the needle shield 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 pull 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® PFS, 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 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® PFS 75 IU, 3 vials of Fostimon® PFS 150 IU, or 2 vials of Fostimon® PFS 225 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 syringes should be disposed of in an appropriate container).

7. MARKETING AUTHORISATION HOLDER
Please check availability and marketing authorisation details in your country.

8. MARKETING AUTHORISATION NUMBER(S)
Please check availability and marketing authorisation details in your country.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Please check availability and marketing authorisation details in your country.

10. DATE OF REVISION OF THE TEXT
Please check availability and marketing authorisation details in your country.

11. CONDITIONS OF PRESCRIPTION AND DISPENSING
Please check availability and marketing authorisation details in your country.

12. DISCLAIMER
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Full list of trade names:

Fostimon® AT, BE, BG, CH, CY, CZ, DK, FI, FR, IE, IT, LU, NL, NO, PL, SE, UK

Fostimon® HP HU, SK

Altermon® EL

Fostipur® ES

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