Meriofert®

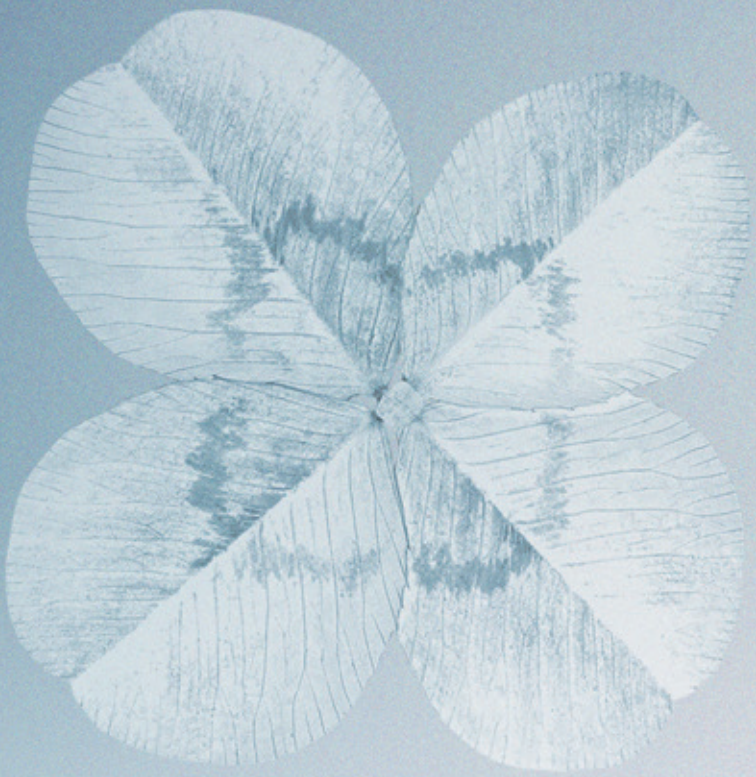
Highly Purified Menotrophin

When Nature meets Innovation

Prescribing information on page 17.

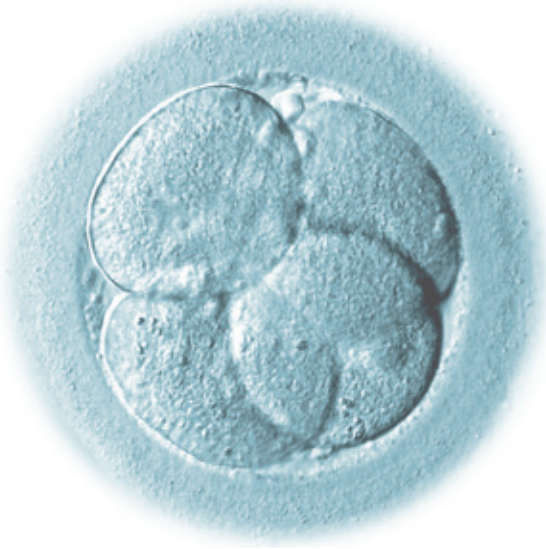
IBSA

Caring Innovation



Meriofert®

Highly Purified Menotrophin



An effective option in the world of infertility treatments[1,2]

AN ORIGINAL FORMULA

Meriofert®'s formula is the first to use highly purified hFSH in concert with highly purified placental hCG sourced from the urine of pregnant women[1].

A CHOICE OF EFFICIENCY

Clinical studies show that **Meriofert®** is an efficient and reliable alternative to current marketed hMG preparations, enabling reduced drug consumption and treatment duration while retrieving a higher number of mature oocytes and cleaved embryos[2,3].

A RELIABLE ALLY

Recognising the crucial role played by the carbohydrate moiety in the FSH and hCG molecules, IBSA designed a natural, chemically non-aggressive purification protocol that manufactures FSH and hCG in parallel processes, effectively preserving balanced glycosylation and ensuring the highest levels of purity and quality[4].

IBSA

AN ORIGINAL NATURAL FORMULA

Helping nature take its biochemical course

IBSA's Highly Purified Menotrophin (HP-hMG) preparation **Meriofert®** contains 75 IU (or 150 IU) follicle stimulating hormone (FSH) and luteinising hormone activity (LH/hCG) per vial[1]. Unlike other marketed HP-hMG preparations, in which FSH and LH/hCG (luteinising hormone and human chorionic gonadotrophin) from pituitary origin, both extracted from urine of menopausal women are present[5], **the LH activity promoted by Meriofert® is mainly provided by highly purified hCG of placental origin and is therefore sourced from the urine of pregnant women (Figures 1 and 2)[1].**

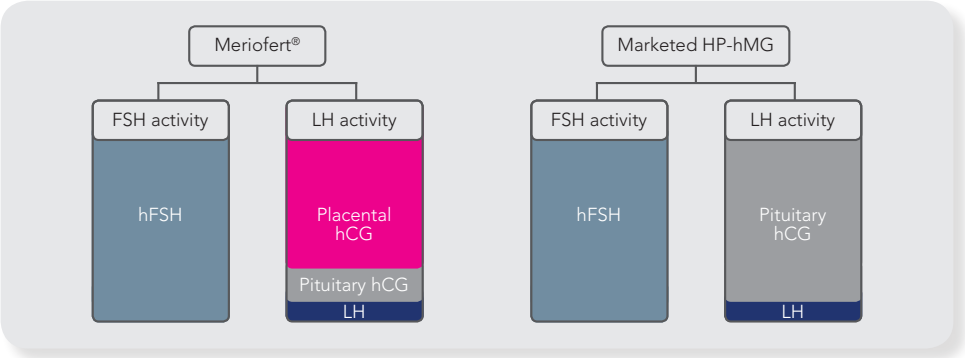


Fig. 1. Schematic representation of Meriofert®'s original natural formula and comparison with other marketed HP-hMG
(Adapted from textual data from ref. 1,5)

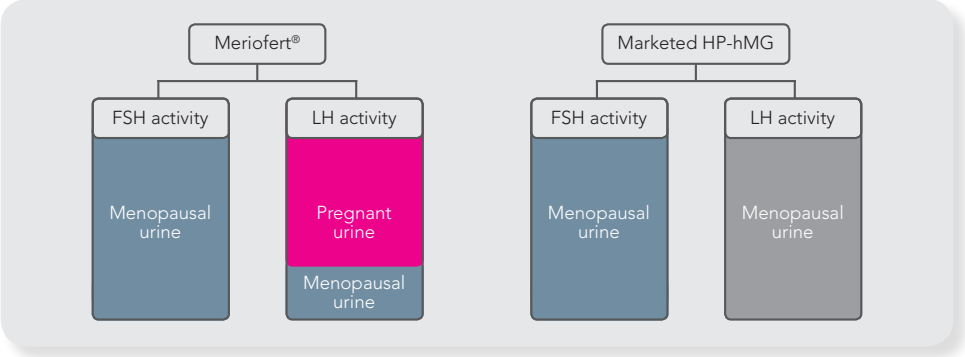


Fig. 2. Scheme of the different sources of gonadotrophins: Meriofert® vs. the market reference
(Adapted from textual data from ref. 1,5)

The LH activity promoted by Meriofert® is mainly provided by highly purified hCG of placental origin and is therefore sourced from the urine of pregnant women[1]. The hCG fraction of pituitary origin is extracted from menopausal urine[5].

hCG, a multifaceted molecule

GLYCOSYLATION OF hCG

hCG is a highly glycosylated molecule: 70% of its structure is represented by the peptide, and 30% by carbohydrate residue (oligosaccharides)[6].

The molecule presents 8 different carbohydrate moieties, 6 of which are linked to the β subunit on 2 N- and 4 O- glycosylation sites and 2 linked to α subunit both on an N- glycosylation sites. Owing to variation in the content of terminal sialic acid of its oligosaccharides, hCG displays extensive charge heterogeneity with isoelectric point (pI) values ranging from 3 to 7 (Fig 3.)[6,7].

The secretion, biological activity and half-life *in vivo* of hCG are highly dependent on the glycosylation status of the molecule.

Indeed, the sialic acid content of hCG plays a key role in its receptor binding ability, biological activity and clearance from circulation[6].

Furthermore, the β subunit of hCG shows an amino acid sequence similar to LH, however a notable difference is the presence of a long carboxy-terminal segment containing the four O-linked oligosaccharide residue, **the so called hCG "tail"**. In addition, hCG β-subunits contain two N-linked glycosylation sites, compared with LH's single site[7].

Because of its higher number of both glycosylation sites and sialic acid residues compared with LH, **hCG exhibits a markedly longer half-life *in vivo*** compared to LH[7,8].

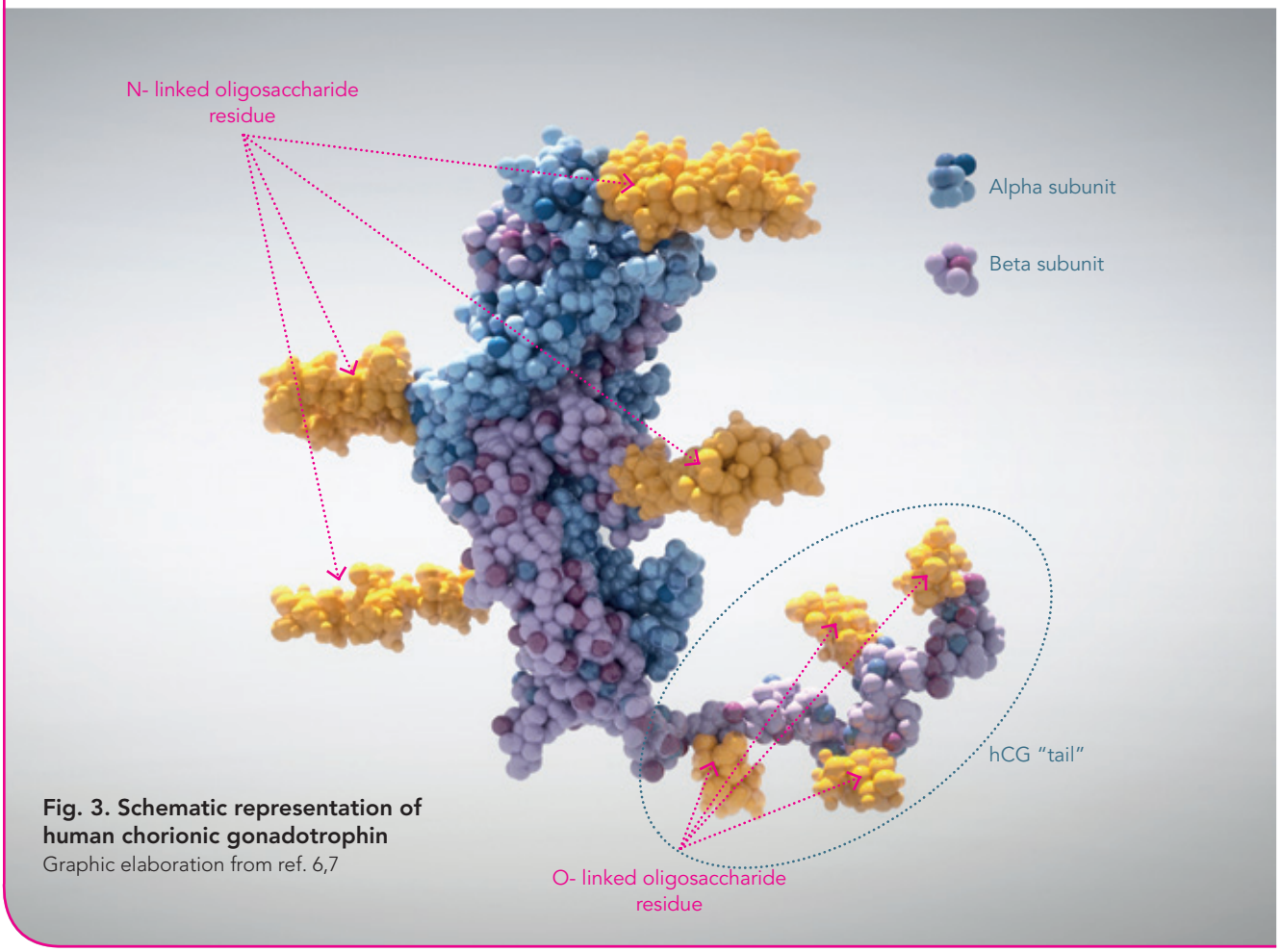


Fig. 3. Schematic representation of human chorionic gonadotrophin
Graphic elaboration from ref. 6,7

hCG EXISTS IN SEVERAL DIFFERENT BIOLOGICALLY ACTIVE VARIANTS

Once considered as a single molecule, today the term hCG refers to both a family of independent, similarly-structured molecules and a variety of blood and urine breakdown products. Actually, there is a family of hCG variants with identical aminoacid sequences but differing in the glycosylation type and rate produced by different cells that show independent functions[9].

PLACENTAL hCG

hCG s the first hormonal message from the placenta-the trophoblast - towards the mother.
Indeed, it is detectable in maternal blood as early as two days after implantation (about one week after fecundation) and is used in pregnancy diagnosis[6].

Placental hCG has an essential role in pregnancy and maternal adaptation since it promotes the trans-formation of cyclic ovary *corpus luteum into gravid corpus luteum* enabling the maintenance of ovarian progesterone, estradiol and estrone secretion during the first six weeks of pregnancy. hCG acts like a superagonist of LH by stimulating corpus luteal cells through the LH/CG receptor (LHCGR), until the steroidogenic activity of the fetal-placental unit compensates the maternal ovarian functions[6].

The placental hCG is produced mainly by the syncytiotrophoblast - the epithelial covering of the highly vascular embryonic placental villi - which invades the wall of the uterus to establish nutrient circulation between the embryo and the mother. 99% of it is secreted in maternal blood from week 2 of pregnancy and peaks around 10-12 gestational weeks (Figure 4)[6,7].

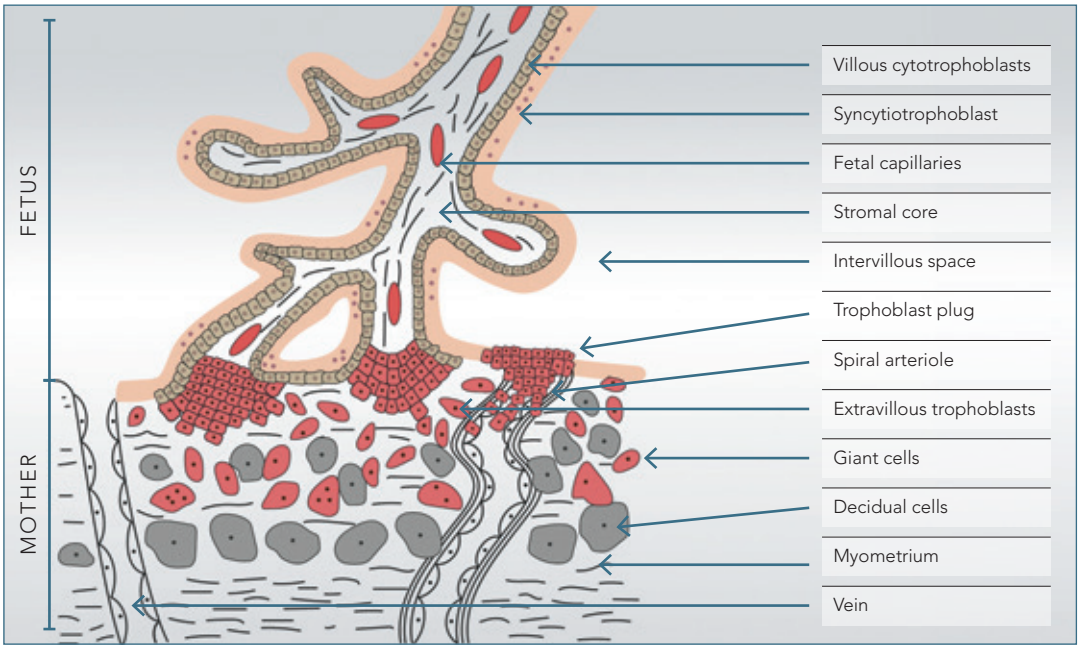


Fig. 4. Schematic representation of a chorionic villus at the implantation site
(Adapted from fig. 1 ref. 10)

hCG, a multifaceted molecule

PITUITARY hCG

In women, hCG is also produced by the pituitary gland during the menstrual cycle (independently from the pregnancy status) and it controls steroidogenesis and follicular ovulation[8].

Typically, the pituitary is able to produce a certain amount of sulfated hCG, thanks to a specific enzyme, GalNac transferase, that binds a terminal sulfate residue on the glycan side-chain instead of the usual sialic acid residue[8].

As a consequence of the sulfonation, the *in vivo* clearance rate of the sulfated hCG is increased in comparison to sialylated hCG (such as the placental hCG) because of the high affinity of liver receptors for the sulfated residue[8].

Previous *in vitro* studies on the characterization of the pituitary hCG (Birken) displayed both a lower biological activity and receptor binding potency of pituitary hCG in comparison to hCG purified from pregnant women (placental hCG)[8].

Consistently, the same authors reported that the sialic acid content of the pituitary hCG is less than that of the placental hCG while the sulfate concentrations are well represented, as shown in table 1.:

Table 1. Comparative sulfate content of pituitary and placental hCG subunits (Adapted from tab. 1 ref. 8)

Protein	Sulfate content (mol/mol)	Sialic acid (mol/mol)
Pituitary hCGα	0.8	1.7
Pituitary hCGβ	2.7	4.6
Placental hCGα	0.4	2.4
Placental hCGβ	0.4	9.4
Placental hCG	0.4	15.6

In menopause, with the absence of steroid feedback to the hypothalamus, GnRH pulse becomes maximal. The result is the promotion of vast excesses of LH, hCG and FSH to be produced by gonadotropic cells. **Pituitary sulfated hCG is thereby easily detectable in menopausal women[8,9].**

hCG is a multifaceted molecule with different biologically active variants. Pituitary hCG controls steroidogenesis during the menstrual cycle and is typically sulfated[8]. It is highly detectable in menopausal women. Placental hCG is essential for pregnancy maintenance and is detectable in pregnant urine only[6,7].

Follicle stimulating hormone

Similarly to hCG, the follicle-stimulating hormone (FSH) is a member of the glycoprotein hormone family (GPH) and is thus composed by two non-identical proteic α and β subunits, each having two possible N-linked glycosylation sites (Figure 5) for the oligosaccharide residue chains.

Consequently, FSH is comprised by a family of isohormones or **isoforms** which differ in their ionic charge due to variance in their oligosaccharide structure (carbohydrates) that includes differences in the number of charged terminal sialic acid[11].

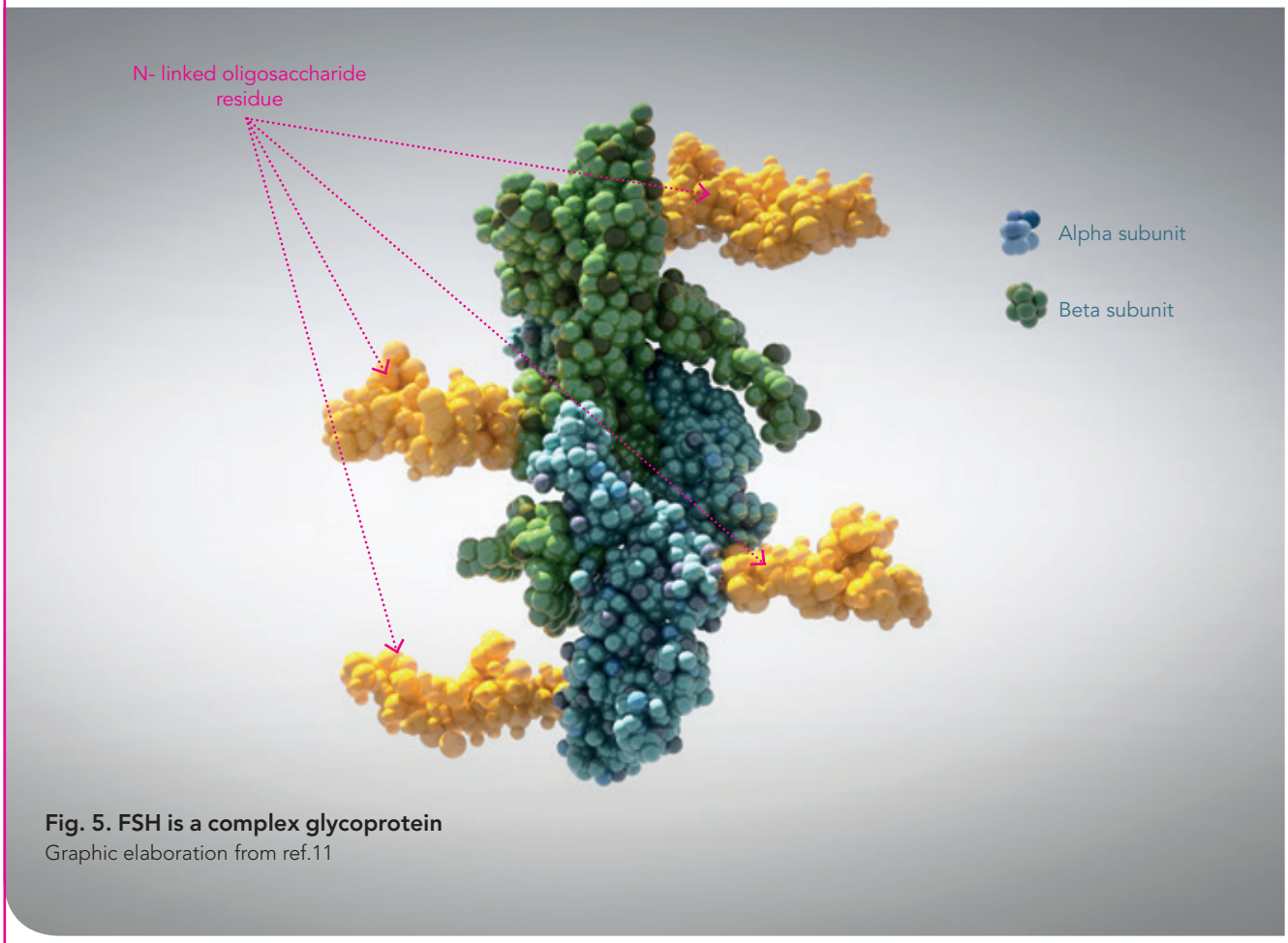


Fig. 5. FSH is a complex glycoprotein
Graphic elaboration from ref.11

The higher the number of carbohydrates branches (or antennae) and of sialic acid residues linked to the proteic backbone of FSH, the higher the acidity of the molecule (Figure 6). Actually, **in humans 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 the heterogeneity of FSH[12].

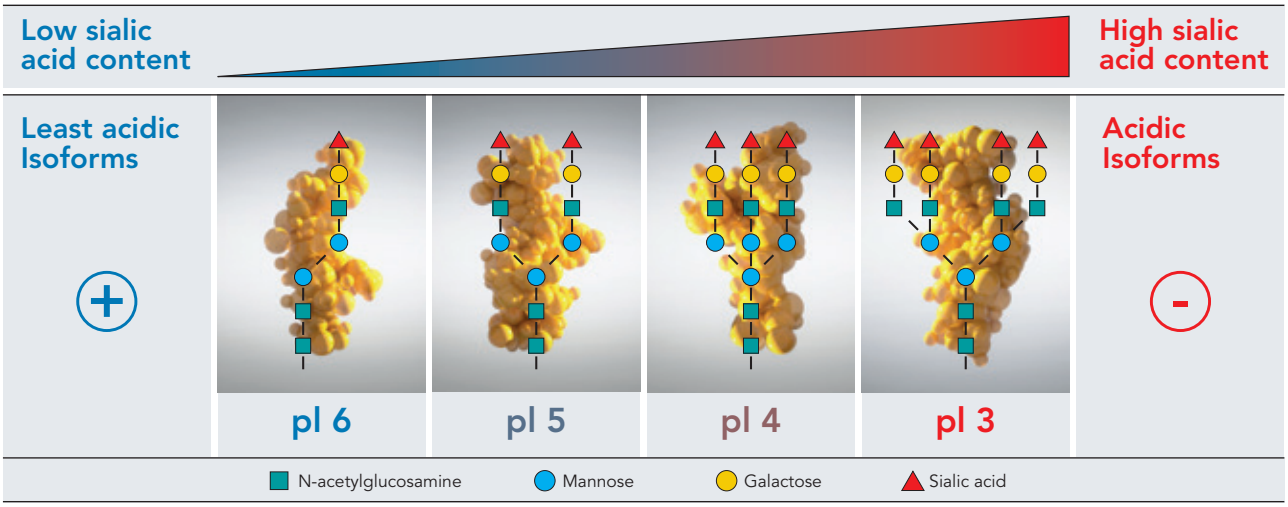


Fig. 6. Schematic representation of the human pituitary range of FSH isoforms according to the isoelectric point (pI) (Adapted from textual data from ref. 4)

IBSA's highly purified FSH contained in Meriofert® was fully characterized in a recent study[4], accurately recording the number of antennae, the composition and the completeness of the glycan moieties present in the FSH active compound.

The results show the prevalence in IBSA's highly purified FSH of more acidic isoforms from species containing greater quantities of sialylated and branched carbohydrate moieties. By contrast, the less acidic isoforms observed for the recombinant glycoproteins contain less sialic acid and a prevalence of diantennary species.

As reported in table 2, the estimated quantitative presence of sialic acid (Z number) resulted the highest for IBSA's highly purified FSH compared to recombinant FSH (recFSH).

Table 2. Oligosaccharide composition and estimated charge number (Z) of IBSA's HP-hFSH and two recombinant preparations (Adapted from tab. 6 ref. 4)

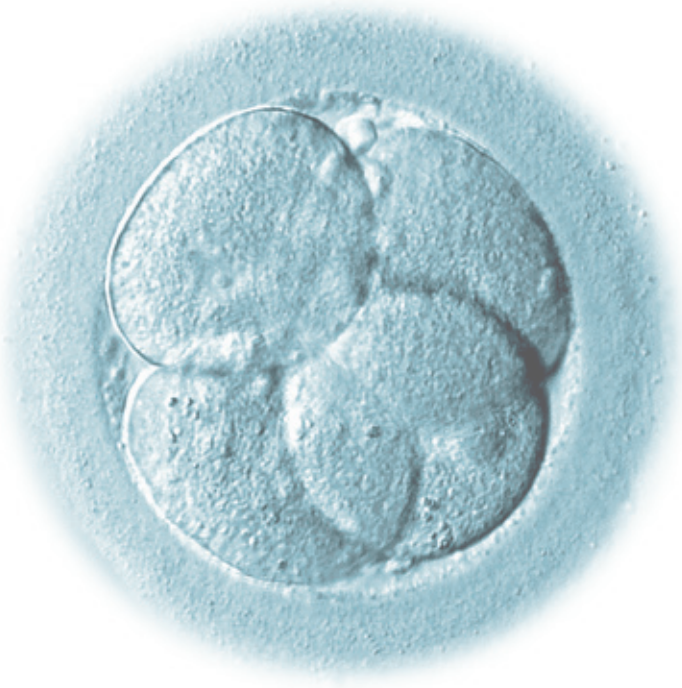
Glycan type	Relative amount %		
	IBSA	recFSH	recFSH
Asialoglycan	2.1	4.6	12.6
Monosialylated	5.1	23.3	43.3
Disialylated	41.6	45.1	33.4
Trisialylated	35.7	19.8	8.6
Tetrasialylated	15.5	7.2	2.0
Estimated Z Number	**257**	**202**	**144**

This study conclusively proves that IBSA's patented protocol, specifically designed to extract FSH from human urine, indeed **preserves the glycosylation status of the molecule throughout every step and minimizes the possible degradation of the oligosaccharide moieties[4].**

FSH is a complex glycoprotein made up by a variety of isoforms with different biological roles. The highly purified FSH fraction contained in Meriofert® is enriched with acidic isoforms thanks to IBSA's exclusive purification protocol, which preserves the natural glycosylation status of the molecules[4].

A CHOICE OF EFFICIENCY

The confidence of clinical data



Randomised, controlled clinical studies suggest that Meriofert® is an efficient alternative in the setting of assisted reproduction (ART) as it reduces drug consumption and treatment duration while retrieving more oocytes and cleaved embryos, and may provide additional practical advantages in the management of ART procedures[2-3].

Italian study

A prospective, randomised, investigator-blind, controlled, clinical study on the clinical efficacy and tolerability of two highly purified hMG preparations administered subcutaneously in women undergoing IVF Alviggi C *et al.* - Clinicaltrials.gov: NCT00335894[3]

OBJECTIVE

The aim of this multicenter, prospective, randomised, investigator-blind, controlled clinical trial was to evaluate the clinical efficacy and tolerability of **Meriofert®*** compared to marketed reference HP-hMG (Menopur-Ferring) when administered to patients undergoing controlled ovarian stimulation (COS) for IVF, with or without ICSI. This was the first-ever truly randomised controlled trial comparing the safety and the clinical efficacy of two highly purified hMG preparations.

** to notice that in this paper **Meriofert®** takes the brand name of Merional HG*

SETTINGS

Three fertility clinics in Italy participated in this randomised trial between March 2006 and May 2008. One hundred fifty-seven patients were randomised in a 1:1 ratio, according to a computer-generated list, in two parallel groups: 78 started COS with **Meriofert®** and 79 with Menopur.

Enrolled patients [mean age 31.8 (3.7) years for **Meriofert®** and 32.6 (2.9) years for Menopur] underwent a standard, long down-regulation protocol using GnRH agonist. In both groups, a starting hMG dose of 225 IU was maintained for the first 4 - 5 days.

RESULTS

Results of the study (Table 3) showed that both highly purified hMG preparations were equivalent in terms of number of oocytes retrieved (primary endpoint: 8.8 ± 3.9vs 8.4 ± 3.8, p = 0.54).

In the patients treated with Meriofert®, a higher occurrence of mature oocytes (78.3% vs 71.4%, p = 0.005) was observed **and a reduced quantity of gonadotrophins administered per cycle** (2,556 ± 636 IU vs 2,969 ± 855 IU, p<0.001). Fertilization, cleavage and implantation rates, number of positive β-hCG (pregnancy) tests, and clinical pregnancy rate were comparable in the two groups. Both treatments were well tolerated.

One limitation of this study was that the oocyte fertilization procedure and embryo transfer had to be performed in compliance with the Italian legislation on assisted reproduction in force at the time of the study (Legge 40/2004); according to this law (later modified by the Italian Supreme Court), no more than 3 oocytes per patient were inseminated and all the available embryos were transferred. No oocytes, 2PN zygotes or embryos were frozen and no embryo was discarded. There was no significant difference in the number of mature oocytes microinjected, and the fertilization and cleavage rates were comparable between the treatment groups. Before transfer, embryos were scored according to the criteria established by Veeck, showing no differences between treatment groups.

The implantation rate per embryo transfer, the positive β-hCG (pregnancy) test and the clinical pregnancy rate were equivalent between treatment groups. The occurrence of relevant complications such as OHSS and miscarriage was similar in patients treated with **Meriofert®** or Menopur.

CONCLUSIONS

The results of this study support the efficacy and safety of **Meriofert®** given subcutaneously for assisted reproduction techniques. **Efficiency of Meriofert® appears to be higher due to the reduced quantity of drug used and the higher yield of mature oocytes retrieved**.

In summary, **Meriofert®** and Menopur were proven to be equally effective in achieving proper outcome of ART. **Meriofert® appears to be more efficient than Menopur in this setting as it reduces drug consumption and treatment duration** and may provide additional practical advantages in the management of ART procedures.

Italian study

	N	Meriofert®	N	Menopur	p value[a]
COS duration (days)	78	11.3 (1.5)	79	12.3 (2.1)	<0.001
hMG units, total	78	2555.8 (635.9)	79	2968.7 (854.8)	<0.001
hMG units, daily	78	224.2 (37.0)	79	238.6 (48.7)	0.04
Ratio MII/Total oocytes retrieved (%)	72	78.3	73	71.4	0.005
Ratio Immature/Total oocytes retrieved (%)	72	20.4	73	26.3	0.01
Nr of inseminated oocytes	72	2.7 (0.7)	73	2.7 (0.7)	0.42
Fertilization rate[a]	70	88.5	72	92.5	0.18
Positive β-hCG test, n		25		27	-
/ OPU, %	72	34.7	73	37.0	0.78
/ transfer, %	67	37.3	72	37.5	0.98
Implantation rate[b] %	67	15.7	72	15.4	0.94
Clinical pregnancies, n		20		20	-
/ OPU, %	72	27.8	73	27.4	0.96
/ transfer, %	67	29.9	72	27.8	0.79
Abortion rate, n (%)		1 (5.0)		2 (10.0)	-

Table 3. Stimulation and fertilization parameters (Adapted from tab. 2 ref. 3)
Note: Where not specified, data are expressed as mean (SD)
[a] Fertilization rate and cleavage rate calculated per inseminated oocyte
[b] Implantation rate defined as the total number of gestational sacs divided by the total number of embryos transferred.

European study

A randomised, controlled trial comparing the efficacy and safety of a new hMG preparation to a reference product in patients undergoing controlled ovarian stimulation for in vitro fertilization.
Lockwood *et al.* - Clinicaltrials.gov: NCT01312766[2]

OBJECTIVE

The aims of this prospective, investigator-blind, randomised, controlled, parallel-group, multicenter study were to confirm the non-inferiority of **Meriofert®** compared to Menopur with regard to clinical outcome (the primary endpoint being the total number of oocytes retrieved), and **to compare the incidence of clinically significant ovarian hyperstimulation syndrome (OHSS) according to Golan Criteria in patients treated with Meriofert® compared to patients treated with Menopur.**

SETTINGS

270 women undergoing in vitro fertilization (IVF) were randomised from March 2011 through April 2013. Women aged 18-40 years (mean age 33.3 (4.0) and 33.0 (4.1) for **Meriofert®** and Menopur respectively), with BMI ≤30 kg/m2 and <3 prior completed assisted reproductive technology (ART) cycles, exhibiting baseline (day 2-3) FSH <10 IU/L and E2 <80pg/ml, undergoing IVF at 6 centers in 5 European countries, were enrolled. Standard long down-regulation with GnRH-agonist was performed before starting COH. After confirmation of down-regulation, patients were randomised to one of the two treatment groups and were instructed on self-administration and supplied with the assigned medication, with the first dose set at 150 IU for patients aged ≤35 years or 225 IU for patients aged >35 years and commenced 0 to 3 days following confirmation of down-regulation.

MAIN RESULTS

Primary endpoint: Total number of oocytes

In the ITT population, **the mean (±SD) number of oocytes retrieved was significantly higher (P <0.05) in women stimulated with Meriofert® (11.6±6.6) than in those stimulated with Menopur (9.7±5.9) (Table 5).** The difference [**Meriofert®**–Menopur] in mean number of oocytes retrieved was +1.9, with a 95% CI of the difference equal +0.43 to +3.43 (i.e. a 95% CI lower limit greater than the predefined clinically significant difference of -2.1). These results were confirmed in the PP analysis, for which the total number of oocytes retrieved was 12.3±6.2 in the **Meriofert®** group and 10.1±5.7 in the Menopur group.

Secondary endpoints:

No statistically significant differences between **Meriofert®** and Menopur were seen for implantation rate and pregnancy outcome parameters: positive serum pregnancy test rate, clinical pregnancy rate, delivery and live birth rate (Figure 7). Although there was no statistically significant difference in the total and mean daily units of hMG used (Table 4), **the duration of the stimulation was shorter in the Meriofert® group. The increased number of oocytes and mature (MII) oocytes retrieved in the Meriofert® group was also associated with an increased number of cleaved embryos obtained** (Table 4). This significantly higher yield obtained with Meriofert translated into a higher number of cryopreserved embryos available for subsequent transfer. The cumulative pregnancy rates were 46% (n=58/126) and 43% (n=56/129) respectively, for the PP population (Figure 7).

DISCUSSION

The use of **Meriofert®** led to retrieving more oocytes, MII oocytes and cleaved embryos in ART than in a classical hMG reference. **Our results are concordant and confirm the results of a prior study[3] showing that Meriofert® had shorter COS that used less drug while providing a similar oocyte yield.** In this study, with the same quantity of drug and again a shorter stimulation period, significantly more oocytes were retrieved in the **Meriofert®** group.

CONCLUSIONS

The strength of this study resides in the randomised controlled trial which validates its result: more oocytes retrieved with the new hMG preparation. The fact that this difference also translates into more mature oocytes and embryos being obtained suggests that the new hMG preparation may also foster higher cumulative IVF outcome. However the study was not powered for comparing pregnancy rates obtained with the two hMG preparations, thus additional studies should be performed to confirm these findings. **In light of the results obtained in this RCT, Meriofert® is an effective alternative for controlled ovarian stimulation in IVF cycles. As suggested by the National Institute for Clinical Excellence (NICE)[13], the choice of gonadotrophin should depend upon availability, patient convenience and cost-effectiveness. In undertaking this calculation, the total amount of drug needed and the duration of stimulation should be important parameters.**

Variable	Meriofert® (N=135)	Menopur (N=135)	P value*
Total hMG units, Mean (IU)	2171.4 (980.0)	2303.6 (906.4)	NS
COH duration (days)	10.2 (1.3)	10.6 (1.5)	0.02
Oocytes retrieved, total (n)	11.6 (6.6)	9.7 (5.9)	0.012
Mature (Grade III-metaphase II) oocytes (n)	10.3 (6.0)	8.2 (5.1)	0.002
Ratio MII/Total oocytes retrieved (%)	85.0	80.9	0.004
Inseminated-injected oocytes, (IVF + ICSI) (n)	10.8 (5.9)	8.4 (5.0)	<0.001
Cleaved embryos on day 2 (n)	5.8 (3.8)	4.8 (3.7)	0.04
Implantation rate, %	29.1 (41.0)	28.2 (36.9)	NS

Table 4. Stimulation and fertilization parameters (ITT population) (Adapted from Lockwood)[2]
ITT, intention to treat population; n=135 in the Meriofert group; n=135 in the Menopur group
Data are reported as (mean ± SD) if not otherwise specified.
ICSI, intracytoplasmic sperm injection; NS, not statistically significant.
* F-test (analysis of variance) for continuous variables, Fisher's exact test for categorical variables.

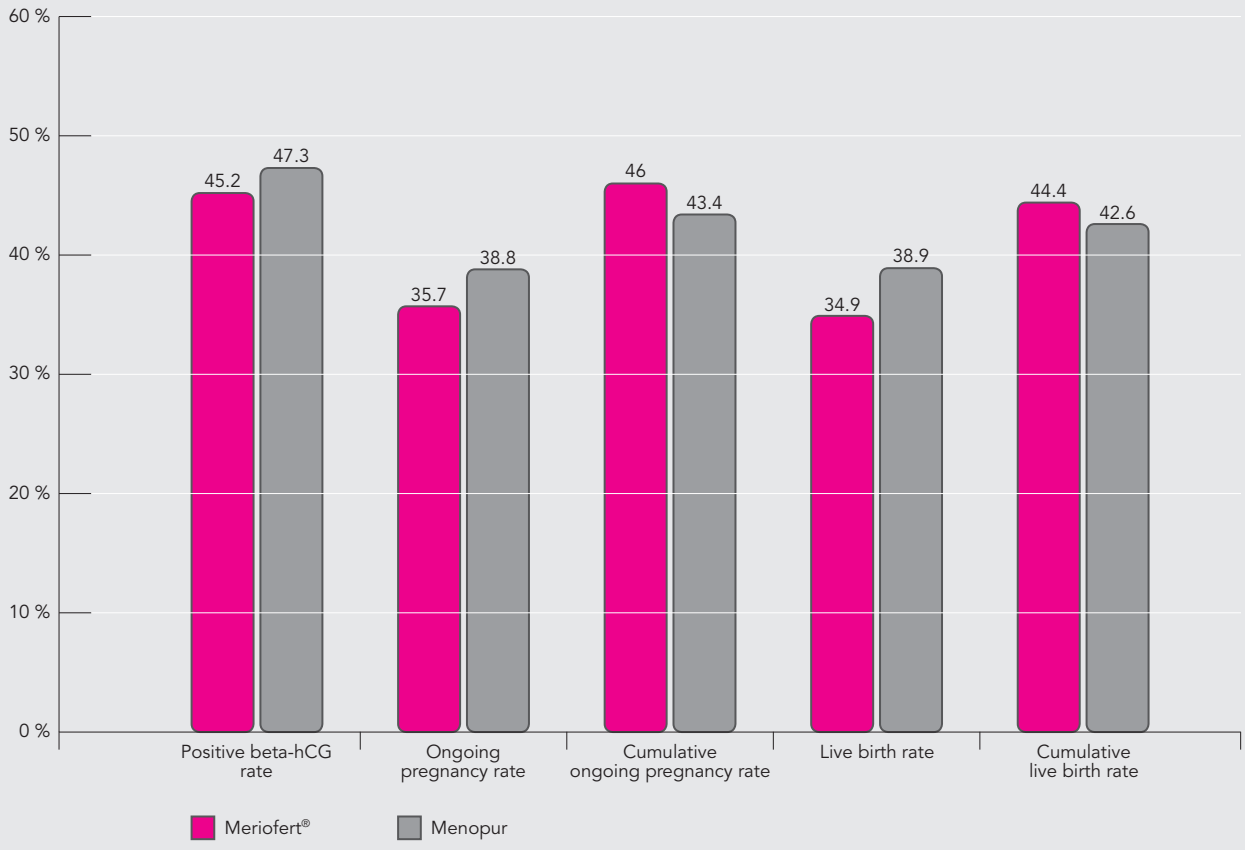


Figure 7. Pregnancy outcomes (PP population) (Adapted from fig. 2B ref. 2)
PP, per protocol population; n=126 in the Meriofert group; n=129 in the Menopur group.
P-value not statistically significant for any of the parameters (Fisher's exact test for categorical variables).

Investigator-initiated study on real-world effectiveness of Meriofert® treatment in women undergoing ART

DESIGN AND SETTING

Retrospective, longitudinal, non-interventional cohort study[14] including anonymized data of women undergoing ovarian stimulation for IVF or ICSI with Meriofert® during an 18-month period. Data were collected from the electronic patient databases of 12 French ART centres. The main outcome was number of oocytes retrieved. All data were categorized according to female age (<25, 25–29, 30–34, 35–37, 38–39 and >39 years), see table 5.

RESULTS

A total of 1006 cycles from 914 women treated with Meriofert® were included. At the time of first ovarian stimulation in the study, women were 34.9 ± 5.0 years old, with a median body mass index of 22.7 kg/m². Couples had been infertile for more than 4 years, with all patterns of causes of infertility. A median total dose of 2700 IU (from 1500 IU in the group of women aged less than 25 years old to 3000 in the group of women aged over 39 years old) was recorded. The mean number of oocytes retrieved per cycle was 9.5 ± 6.8, and the mean number of mature oocytes per cycle was 7.4 ± 5.5. The obtained ongoing pregnancy per started cycle was 26.0% (95% confidence interval CI: 24.1–27.9) and the obtained ongoing pregnancy per puncture was 27.0% (95% CI: 25.0–29.0).

CONCLUSIONS

This is the first cohort study to describe Meriofert® treatment management in real-life conditions. The real-world data show that Meriofert® is an effective option for ovarian stimulation.

	<25 years	25–29	30–34	35–37	38–39	>39 years	Total
No. of cycles	24	132	279	228	132	211	1006
Ovarian stimulation duration, days (median [IQR])	10 [8–11]	10 [9–11]	10 [9–11]	10 [9–12]	10 [10–11]	10 [9–11]	10 [9–11]
Start gonadotrophin dose, IU (median [IQR])	150 [150–225]	188 [150–225]	225 [150–300]	300 [200–300]	300 [225–300]	300 [300–300]	300 [150–300]
Total gonadotrophin dose, IU (median [IQR])	1500 [1238–2175]	1800 [1350–2325]	2250 [1538–3000]	2700 [2025–3525]	3000 [2400–3600]	3000 [2250–3600]	2700 [1800–3300]
No. of oocyte retrievals	24	127	266	221	131	194	963
No. of oocytes retrieved per retrieval (mean ± SD)	16.0 ± 8.1	13.5 ± 9.9	10.0 ± 5.9	9.1 ± 6.0	7.8 ± 5.7	6.8 ± 4.6	9.5 ± 6.8
No. of mature oocytes per puncture (mean ± SD)	12.7 ± 7.5	10.1 ± 7.3	8.0 ± 5.2	7.1 ± 4.9	6.1 ± 4.9	5.3 ± 3.8	7.4 ± 5.5
Fertilization rate, % (mean ± SD)	66.4 ± 17.1	66.5 ± 26.7	70.8 ± 25.8	68.2 ± 28.1	67.0 ± 29.2	66.5 ± 30.3	68.1 ± 27.7
No. of viable embryos (mean ± SD)	3.3 ± 2.4	3.5 ± 2.7	3.2 ± 2.5	2.3 ± 1.5	2.5 ± 1.8	2.4 ± 1.7	2.8 ± 2.1
No. of transfers	24	137	265	192	111	168	897
Fresh, n (%)	19 (79.2)	88 (64.2)	190 (71.7)	165 (85.9)	93 (83.8)	139 (82.7)	694 (77.4)
Frozen–thawed, n (%)	5 (20.8)	49 (35.8)	75 (28.3)	27 (14.1)	18 (16.2)	29 (17.3)	203 (22.6)
Ongoing pregnancy (%) [95% CI]							
Per started cycle	46.0% [31.8–60.2]	35.0% [29.2–40.8]	31.0% [27.1–34.9]	26.0% [21.9–30.1]	23.0% [17.9–28.1]	14.0% [10.7–17.3]	26.0% [24.1–27.9]
Per oocyte retrieval	46.0% [31.8–60.2]	36.0% [30.0–42.0]	32.0% [28.0–36.0]	27.0% [22.8–31.2]	24.0% [18.8–29.2]	15.0% [11.4–18.6]	27.0% [25.0–29.0]

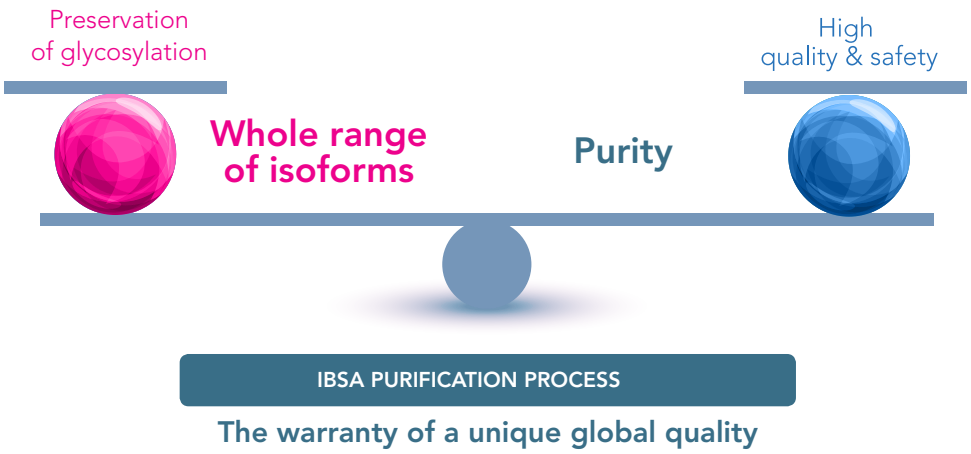
Table 5. Cycle characteristics and clinical outcomes of study population according to the female age group and overall population (Adapted from tab. 2 ref. 14)

CI = confidence interval; GnRH = gonadotrophin-releasing hormone; IQR = interquartile range.

A RELIABLE ALLY IN ART PROGRAMS

The case for unparalleled purity

By recognising the pivotal role of carbohydrate components in both the FSH and hCG molecules, IBSA has designed and patented an innovative, non aggressive purification process that maintains the ideal natural glycosylation balance and reaches the highest levels of purity and quality. Unlike other marketed hMG preparations in which post-menopausal urine is the only manufacturing source, **the Meriofert® starting material is urine collected both from pregnant and post-menopausal women[1], enabling a parallel, step-by-step purification process that preserves the carbohydrate moieties of the molecule and yields unparalleled purity for both the FSH and hCG components[4,15].**



(Graphic elaboration of textual data from ref. 4)

Based on the most advanced technology and know-how of the structure-function of gonadotrophins, IBSA's purification process provides a **benchmark of high quality and safety** for the obtainment of the **highest purity** and **a full range of gonadotrophins molecular species[4].**

IBSA's state-of-the-art, non-aggressive purification process preserves the natural glycosylation balance of its components while guaranteeing unparalleled purity levels[4].

Performed all-in-house under the same global quality assurance system, the process workflow[15] includes:

- Urine collection
- Early purification
- Final purification

STEP 1

URINE COLLECTION AND EARLY PURIFICATION

Urines are collected under IBSA's direct responsibility applying an internationally approved GMP quality system. The initial purification steps were designed to reduce the load of proteins and other small urinary. It includes selective precipitation and solubilisation under mild conditions in order to eliminate some urinary components and to preserve the molecular structure of the FSH and the hCG. This enables avoiding the use of further harsh solvents or chemicals to reach the targeted purity. Early purification also includes some validated virus-cleaning steps which efficiently eliminate or inactivate viruses which could be theoretically present in the initial urines.

STEP 2

FINAL PURIFICATION

The final purification steps include a series of chromatographies which enable recovery of the whole range of the FSH and hCG isoforms, eliminating the urinary impurities.

In particular, the **Blue Sepharose chromatography is performed on an affinity resin, based on a patented, innovative concept that** allows high selectivity in separating the different protein species and extended recovery of all the natural species, **thus resulting in an extremely highly purified product (Figure 8)[1].**

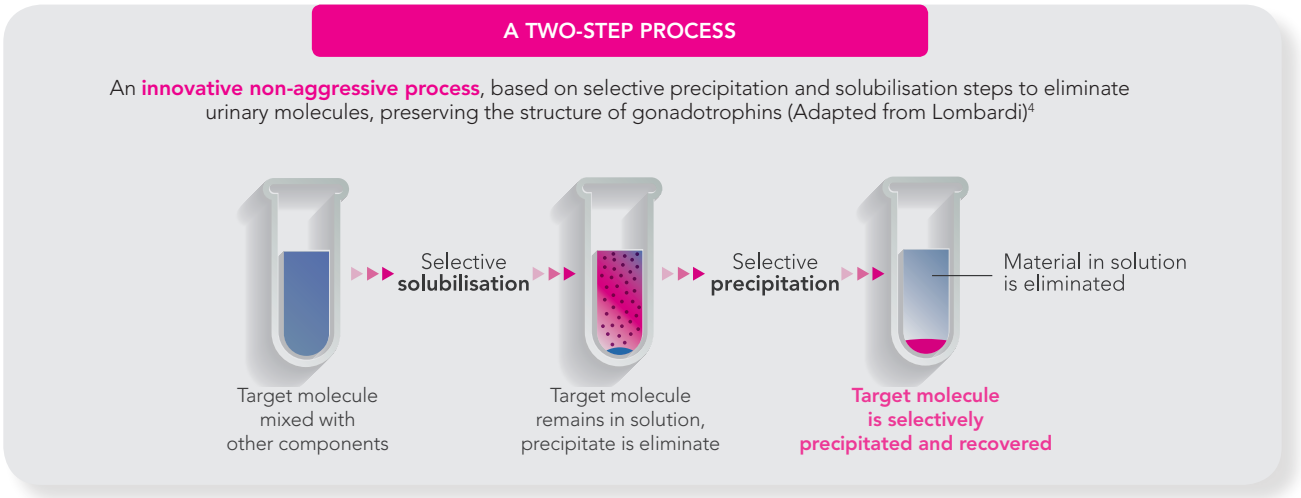


Fig. 8. Schematic representation of the main steps of IBSA's purification process[15]

References

1. Meriofert SmPC
2. G Lockwood *et al.*, A randomised controlled trial comparing the efficacy and safety of two HMG preparations gaining their LH bioactivity from different HCG sources. Reproductive BioMedicine Online. 2017 Jul; 35(1): 17-27.
3. Alviggi C *et al.*, A prospective, randomised, investigator-blind, controlled, clinical study on the clinical efficacy and tolerability of two highly purified hMG preparations administered subcutaneously in women undergoing IVF. Gynecol Endocrinol. 2013 Jul;29(7):695-9.
4. Lombardi A *et al.*, Evaluation of the oligosaccharide composition of commercial follicle stimulating hormone preparations. Electrophoresis 2013;34(16):2394-406.
5. Menopur SmPC.
6. Fournier T *et al.*, Review: hCGs: different sources of production, different glycoforms and functions. Placenta. 2015 Apr;36 Suppl 1:S60-5.
7. Stenman UH *et al.*, The classification, functions and clinical use of different isoforms of HCG. Hum Reprod Update. 2006;12(6):769-84.
8. Birken S *et al.*, Metabolism of hCG and hLH to multiple urinary forms. Mol Cell Endocrinol. 1996 Dec 20;125(1-2):121-31.
9. Cole LA. New discoveries on the biology and detection of human chorionic gonadotropin. Reprod Biol Endocrinol. 2009; 7: 8.
10. Segond N, Transcriptome Analysis of PPARc Target Genes Reveals the Involvement of LysylOxidase in Human Placental Cytotrophoblast Invasion. PLOSONE, www.plosone.org, 2013; 8 (11) e79413.
11. Andersen CY *et al.*, FSH-induced resumption of meiosis in mouse oocytes: effect of different isoforms. Mol Hum Reprod. 1999;5(8):726-31.
12. Timossi CM *et al.*, Differential effects of the charge variants of human follicle-stimulating hormone. J Endocrinol. 2000;165:193–205.
13. NICE, Fertility: assessment and treatment for people with fertility problems. National Institute for Clinical Excellence and National Collaborating Centre for Women's and Children's Health, 2013.
14. Languille S *et al.*, Real-world effectiveness of Fertistartkit® treatment in women undergoing ART in French clinical practice: a retrospective multicentre study. RBMO 2020 https://doi.org/10.1016/j.
15. Data on file.

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, Public 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, Public 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, Public 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

Date of last revision: April 14, 2022

Full list of trade names:

Meriofert®
Fertinorm®
Eigenorm®
Fertistartkit®
Mensinorm®
Merional HG®

Meriofert® Italian price and refundability

Powder and solvent for solution for subcutaneous or intramuscular injection[1].

- 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).