1. NAME OF THE MEDICINAL PRODUCT

MERIONAL 75 IU Powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:
Each one ml vial of Merional 75 IU contains:
75 IU Menotrophin BP (Human menopausal gonadotrophin, HMG) providing 75 IU follicle stimulating hormone (FSH) and 75 IU luteinizing hormone (LH) activity*. Menotrophin is purified from human urine.

*The LH activity may be augmented by the addition of Human chorionic gonadotrophin (hCG) to provide a 1:1 ratio of FSH to LH activities.

For a full list of excipients see section 6.1.

3. Pharmaceutical Form

Powder and solvent for solution for injection
Appearance of the powder: white lyophilised pellet
Appearance of the solvent: clear colourless solution

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Anovulation (including polycystic ovarian disease, PCOD) in women who have been unresponsive to treatment with clomiphene citrate.
- Stimulation of multifollicular development in patients undergoing assisted reproductive technologies (ART) such as *in-vitro* fertilization (IVF), gamete intrafallopian transfer (GIFT) and zygote intrafallopian transfer (ZIFT).
- Merional 75 IU may be given in combination with human Chorionic Gonadotrophin (hCG) for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism.

Merional is indicated for use in adults only.

4.2. Posology and method of administration

Treatment with Merional should be initiated under the supervision of a physician experienced in the treatment of fertility issues.

Males
Male infertility: Spermatogenesis is stimulated with hCG (1,000 to 2,000 IU hCG 2-3 times per week) then Merional (75 IU or 150 IU) is administered 2-3 times per week. This treatment should be continued for at least 3 months before any improvement in spermatogenesis can be expected. Current clinical experience indicates that treatment for at least 18 months may be necessary to achieve spermatogenesis.

Females with anovulation (including PCOD)
The objective of treatment with Merional is to develop a single mature Graafian follicle from which the ovum will be released after the administration of hCG Merional may be given as a course of daily injections. In menstruating patients treatment should be started within the first seven days of the menstrual cycle.

The treatment should be adjusted to the individual patient's response as assessed by measuring follicle size by ultrasound and/or oestrogen secretion. A commonly used regimen commences at 75-150 IU of Merional and is increased according to the patient's response. The maximum daily dose is usually not higher than 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.

When an ideal response is obtained a single injection of 5,000-10,000 IU of hCG should be administered 24-48 hrs after the last Merional injection. The patient should be recommended to have coitus on the hCG injection day and the following day. Alternatively intrauterine insemination (IUI) may be performed.

In the event of an excessive response treatment should be suspended and hCG withheld (see section 4.4). Treatment should recommence in the next cycle at a lower dose than in the previous cycle.

Females undergoing controlled ovarian stimulation for multiple follicular development prior to in-vitro fertilization or other assisted reproductive technologies.

A commonly used protocol for superovulation involves the administration of 150-225 IU of Merional daily commencing on days 2 or 3 of the cycle and continued until sufficient follicular development has been achieved as assessed by monitoring serum oestrogen concentrations and/or ultrasound examination with the dose adjusted according to the patient's response but usually not higher than 450 IU daily. Adequate follicular development is usually achieved by the tenth day of treatment (range 5-20 days).

A single injection of 5,000 IU-10,000 IU of hCG should be administered 24-48 hours after the last injection to induce follicular maturation.

Pituitary down-regulation in order to suppress the endogenous LH surge and to control tonic levels of LH is now commonly achieved by administration of a gonadotrophin releasing hormone (GnRH) agonist. In a commonly used protocol the administration of Merional-is started approximately two weeks after the start of agonist treatment, both being continued until adequate follicular development has been achieved. For example, following two weeks of pituitary down-regulation with an agonist, 150-225 IU Merional are administered for seven days; the dose is then adjusted according to the patient's ovarian response.

Experience with ART indicates that in general the treatment success rate remains stable during the first four attempts and gradually declines thereafter.

Females with anovulation resulting from severe LH and FSH deficiency
In these women (hypogonadotrophic hypogonadism) the objective of Merional treatment is to develop a single mature Graafian follicle from which the oocyte will be released following the administration of hCG. As these women are amenorrhoeic and have low endogenous oestrogen secretion treatment may commence at any time.

The treatment should be adjusted to the individual patient's response as assessed by measuring follicle size by ultrasound and/or oestrogen secretion. A commonly used regimen commences at 75-150 IU of Merional-and is increased according to the patient's response. Should an increased dose of Merional-be deemed appropriate, dose adaptation should preferably be made after 7-14 day intervals and preferably by 150 IU increments. It may be acceptable to extend the duration of stimulation in any one cycle up to 5 weeks.

When an ideal response is obtained a single injection of 5,000 IU-10,000 IU of hCG should be administered 24-48 hrs after the last Merional injection. The patient should be recommended to have coitus on the hCG injection day and the following day. Alternatively intrauterine insemination (IUI) may be performed.

Luteal support may be considered since lack of substances with luteotrophic activity (LH/hCG) after ovulation may lead to a premature loss of the corpus luteum.

In the event of an excessive response treatment should be suspended and hCG withheld (see section 4.4). Treatment should recommence in the next cycle at a lower dose than in the previous cycle.

Paediatric population
There is no relevant use of Merional in the paediatric population in the indications (anovulatory Infertility, females undergoing controlled ovarian stimulation for multiple follicular development prior to assisted reproductive technologies and males with hypogonadotrophic hypogonadism).

Method of administration.
Merional is intended for intramuscular and subcutaneous administration. The powder should be reconstituted immediately prior to use with the solvent provided. In order to avoid injection of large volumes up to 5 vials of Merional 75 IU may be dissolved in one ml of solvent. (see section 6.6 for full details).

Appearance of reconstituted product: The solution must be clear and colourless.

Merional should be reconstituted prior to administration according to the instructions provided in section 6.6.

Patients must be suitably trained in how to handle the product by their physician or other healthcare professional prior to self-administration.

4.3. Contraindications

Merional should not be administered to children or to patients who have:

- Hypersensitivity to the active substance menotrophin or to any of the excipients (see section 6.1)
- Tumours of the hypothalamus or pituitary gland

and to females who have:

- Ovarian enlargement or a cyst not due to polycystic ovarian disease
- Gynaecological haemorrhages of unknown cause
- Ovarian, uterine or mammary carcinoma

Merional should not be used when an effective response cannot be achieved, such as:

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

In males:
- Primary testicular insufficiency.

4.4. Special warnings and precautions for use

Merional is a potent gonadotrophin capable of causing mild to severe adverse reactions and should only be used by physicians who are thoroughly experienced with infertility problems and their management. To minimize the risks of Ovarian Hyperstimulation Syndrome (OHSS) or of multiple pregnancies, ultrasound scans as well as oestradiol measurements are recommended.

Gonadotrophin therapy requires a certain time commitment by physicians and supportive health professionals as well as the availability of appropriate monitoring facilities. In females, safe and effective use of Merional calls for monitoring of ovarian response with ultrasound alone or preferably in combination with measurement of serum oestradiol levels on a regular basis. There may be a degree of interpatient variability in response to menotrophin administration with a poor response in some cases. The lowest effective dose in relation to the treatment objective should be used in both men and women.

Treatment in females
Before starting treatment, the couple's infertility should be assessed as appropriate and putative contraindications for pregnancy evaluated. In particular, patients should be evaluated for hypothyroidism, adrenocortical deficiency, hyperprolactinemia and pituitary or hypothalamic tumours, and appropriate specific treatment given.

Patients undergoing stimulation of follicular growth whether in the frame of a treatment for anovulatory infertility or ART procedures, may experience ovarian enlargement or develop hyperstimulation. Adherence to recommended Merional dosage and regimen of administration and careful monitoring of therapy will minimise the incidence of such events. Accurate interpretation of the indices of follicular development and maturation require a physician who is experienced in the interpretation of such data.

Ovarian Hyperstimulation
OHSS is a medical event distinct from uncomplicated ovarian enlargement. It is a syndrome that can manifest itself with increasing degrees of severity. It comprises marked ovarian enlargement, high serum sex steroids, and an increase in vascular permeability, pleural and rarely in pericardial cavities.

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

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

To minimize the risk of OHSS or of multiple pregnancy, ultrasound scans as well as oestradiol measurements are recommended. In anovulation the risk of OHSS and multiple pregnancy is increased by a serum oestradiol >900 pg/ml (3300pmol/L) and more than 3 follicles of 14 mm or more in diameter. In ART there is an increased risk of OHSS with a serum oestradiol > 3000 pg/ml (11000 pmol/L) and 20 or more follicles of 12 mm or more in diameter. When the oestradiol level is > 5500 pg/ml (20200 pmol/L) and where there are 40 or more follicles in total, it may be necessary to withhold hCG administration.

Adherence to recommended Merional dosage, regimen of administration and careful monitoring of therapy will minimise the incidence of ovarian hyperstimulation and multiple pregnancy (see sections 4.2 “Posology and method of administration” and 4.8 “Undesirable effects”).

In ART, aspiration of all follicles prior to ovulation may reduce the occurrence of hyperstimulation.

OHSS may be more severe and more protracted if pregnancy occurs. Most often OHSS occurs after hormonal treatment has been discontinued and reaches its maximum at about 7-10 days following treatment. Usually, OHSS resolves spontaneously with the onset of menses.

If severe OHSS occurs, gonadotrophin treatment should be stopped if still ongoing, the patient hospitalised and specific therapy for OHSS started.

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

Multiple pregnancy
Multiple pregnancy, especially high order, carries an increased risk of adverse maternal and perinatal outcomes.

In patients undergoing ovulation induction with Merional the incidence of multiple pregnancies is increased as compared with natural conception. The majority of

multiple conceptions are twins. To minimize the risk of multiple pregnancy, careful monitoring of ovarian response is recommended.

In patients undergoing ART procedures the risk of multiple pregnancy is related mainly to the number of embryos replaced, their quality and the patient's age.

The patient should be advised of the potential risk of multiple births before starting treatment.

Pregnancy Wastage
The incidence of pregnancy wastage by miscarriage or abortion is higher in patients undergoing stimulation of follicular growth for ovulation induction or ART than in the normal population.

Ectopic Pregnancy
Women with a history of tubal disease are at risk of ectopic pregnancy, whether the pregnancy is obtained by spontaneous conception or with fertility treatments. The prevalence of ectopic pregnancy after IVF is reported to 2-5% as compared to 1-1.5% in the general population.

Neoplasms of the Reproductive System
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 whether or not treatment with gonadotrophins increases the baseline risk of these tumours in infertile women.

Congenital Malformations
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
In females with generally recognised risk factors for thromboembolic events, such as personal or family history or significant obesity treatment with gonadotrophins may further increase the risk. In these women, the benefits of gonadotrophin administration should be weighed against the risks. It should be noted however, that pregnancy itself also carries an increased risk of thromboembolic events.

Treatment in males
Elevated endogenous FSH levels are indicative of primary testicular failure. Such patients are unresponsive to Merional/hCG therapy.

Semen analysis is recommended 4-6 months after the beginning of treatment in assessing the response.

4.5. Interactions with other medicinal products and other forms of interaction

Concomitant use of Merional with other agents used to stimulate ovulation (e.g. hCG, clomiphene citrate) may potentiate the follicular response, whereas concurrent use GnRH agonists to induce pituitary suppression may increase the dosage of Merional needed to elicit an adequate ovarian response. No other clinically significant drug interactions have been reported.

Merional should not be administered as mixture with other medicinal products in the same injection.

4.6. Pregnancy and lactation

Pregnancy
Merional 75 IU should not be administered during pregnancy. No teratogenic risk has been reported following controlled ovarian hyperstimulation, in clinical use with gonadotrophins. In case of exposure during pregnancy clinical data are insufficient to exclude a teratogenic effect.

Breastfeeding
Merional should not be used during breast-feeding. During lactation the secretion of prolactin can entail a poor response to ovarian stimulation.

Fertility
Merional is used in the treatment of some forms of infertility (see section 4.1 for full details).

4.7. Effects on ability to drive and use machines

Merional has no or negligible influence of the ability to drive and use of machinery. However no studies on the effect on ability to drive and use machines have been performed.

4.8 Undesirable effects

a. Summary of the safety profile

The undesirable effects observed with Merional are generally mild and transitory. The most common adverse reactions are ovarian cysts, injection site reactions and headache occurring in up to 10% of female patients. The most serious adverse reactions are severe OHSS and complications associated with this condition such as ovarian torsion and thromboembolism.

b. Tabulated Summary of adverse events
Within each system organ class, the ADRs are ranked under headings of frequency 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).

Treatment in females

The following table shows the frequency of adverse reactions associated with Merional occurring in patients enrolled in controlled clinical trials and due to spontaneous reporting following post authorisation use

Body system*	Frequency	Adverse Drug Reaction
Nervous system disorders	Very Common	Headache
Vascular disorders	Very rare	Thromboembolism[1,2]
Gastrointestinal disorders	Common	Abdominal pain and gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal cramps and bloating
Skin and subcutaneous tissue disorders	Very rare	Systemic allergic reactions such as (erythema, rash or facial swelling
Reproductive system and breast disorders	Very Common Common Rare	Ovarian cysts OHSS[2] Ovarian torsion[1,2]
General disorders and administration site conditions	Very Common	Injection site reaction[2] such as (pain, redness, bruising, swelling and/or irritation at the site of injection

*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.

[1] Thromboembolism and Ovarian torsion, usually associated with severe OHSS.

[2] See section c

Treatment in males

The following table shows the frequency of adverse reactions associated with menotrophin when used in men; the data is from controlled clinical trials of a competitor product and spontaneous reporting following post authorisation use.

Body system	Frequency	Adverse Drug Reaction
Skin and subcutaneous tissue disorders	Common	Acne
Reproductive system and breast disorders	Common	Gynecomastia
General disorders and administration site conditions	Common	Weight gain.

c. Description of selected adverse reactions

Ovarian Hyperstimulation

See section 4.4

Injection site reactions

Injection site reactions such as (pain, redness, bruising, swelling and/or irritation at the site of injection) are very common but usually non-serious adverse event following the administration of gonadotrophins.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9. Overdose

The effect of an overdose of Merional are unknown, nevertheless one could expect ovarian hyperstimulation syndrome to occur, which is further described in section 4.4. Special warnings and precautions for use.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmatherapeutic group: -Gonadotrophins/human menopausal gonadotrophin
ATC Code: G03GA02

Merional is a preparation of Menotrophin BP (Human menopausal gonadotrophin) obtained from the urine of post-menopausal women.

In women the most important effect resulting from parenteral administration of HMG is the development of mature Graafian follicles.

In men deficient in FSH, Merional administered concomitantly with hCG for at least 4 months induces spermatogenesis.

5.2. Pharmacokinetic properties

HMG is not effective when taken orally and is injected either intramuscularly or subcutaneously. The biological effectiveness of HMG is mainly due to its FSH content. The pharmacokinetics of HMG following intramuscular or subcutaneous administration show great individual variation. According to a study performed with Merional, 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.

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 HMG, following administration, is predominantly renal.

5.3. Preclinical safety data

The gonadotrophins extracted from the urine of post-menopausal women have been used for many years for the treatment of both male and female infertility and in women undergoing medically assisted reproductive techniques. They are regarded as having low toxicity; however no specific studies have been conducted with Merional 75 IU.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Lactose monohydrate

Solvent:
Sterile sodium chloride solution 0.9% w/v

6.2 Incompatibilities

In the absence of incompatibilities studies Merional 75 IU should be diluted with sodium chloride solution only and must not be mixed with other medicinal products.

6.3. Shelf Life

Two (2) Years
For single use only. The reconstituted solution should be used immediately. Any remaining solution should be discarded.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original pack, in order to protect from light.

6.5 Nature and contents of container

Powder in vial: 5 ml clear Type I glass fitted with a butyl rubber stopper and an aluminium seal.
Solvent: 1ml clear Type I glass ampoule

Pack size:
Carton containing 1 vial of Merional 75 IU and 1 ampoule of solvent (1 ml)
Carton containing 10 vials of Merional 75 IU and 10 ampoules of solvent (1 ml)

6.6. Special precautions for disposal

The reconstituted solution is for single use only. It must be used immediately after reconstitution. The solution should be prepared using aseptic technique to minimise contamination.

Instructions for reconstitution:

1. Carefully break the top off the solvent ampoule by snapping it where the red dot is.
2. Aseptically withdraw 1 ml of solvent. As with all parental products inspect the solvent visually for particulate matter or discolouration.
3. Remove the light green coloured flip cap from the Merional vial.
4. Through the rubber septum, slowly inject the solvent solution down the inside of the vial into the white powder.
5. The white powder dissolves immediately without the need to shake the vial.
6. Slowly withdraw the solution into the syringe.
7. If more than one vial of medication is going to be needed to provide the prescribed dose in a single 1ml injection, then slowly inject the solution already in the syringe into the next vial, repeating steps 4-6. The minimum number of vials needed to achieve the intended dose should be used wherever possible to minimise the number of reconstitution operations. Care must be taken when reconstituting more than 1 vial of Merional (in 1 ml diluent) so as to avoid foaming of the reconstituted solution.-If some of the white powder is not in contact with the solvent then gently and slowly roll the vial between the fingers until the powder is completely dissolved. Up to 5 vials of Merional may be dissolved in one ml of solvent. Avoid shaking the vial as this will cause foaming. If excessive foaming does occur discard vial and start again.
8. Merional should be inspected visually for particulate matter or discoloration prior to administration. It should be administered immediately after reconstitution.

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

7 MARKETING AUTHORISATION HOLDER

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

8. Marketing Authorisation Number

PL 21039/0010

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/02/2009

10 DATE OF REVISION OF THE TEXT

06/03/2015