Merional®

Highly purified Human Menopausal Gonadotrophin (HMG) for intramuscular injections

IBSA

Composition

1 vial of active ingredient contains:

Active ingredient:
Human Follicle-Stimulating Hormone (FSH) 75 or 150 I.U.; Human Luteinizing Hormone (LH) 75 or 150 I.U.

Excipient: Mannitol.

Solvent: 2 ml of water for injections.

Properties/Effects

Human Menopausal Gonadotrophin (HMG) is a compound of hormones containing FSH and LH in a ratio of about 1:1. HMG is extracted from the urine of postmenopausal women.
The biological half–life of FSH is slightly longer than that of LH (see paragraph «Pharmacokinetics»), thus conferring HMG a mainly follicle–stimulating activity (FSH).
HMG stimulates the follicular growth and maturation, thus promoting the production of oestrogens.
Therefore, the endometrium is led to proliferation and the implantation and nidation of a fertilized ovum is made possible.

Pharmacokinetics

FSH and LH are eliminated in two phases. In both phases the biological half–life of FSH is longer than that of LH.

The following values have been found in 5 patients submitted to hypophysectomy:

1st phase: FSH about 4 hours, LH about 20 minutes;

2nd phase: FSH about 70 hours, LH about 4 hours.

Indications/Directions for use

Stimulation of follicle maturation in infertile women.

a) Simple follicular stimulation
Hypo– and normogonadotropic anovulation either with or without dysmenorrhea; luteal insufficiency.
In patients partially or completely unresponsive to a treatment with clomiphene.

b) Multiple follicular stimulation
In patients participating in a medically assisted conception program (IVF–ET, GIFT).

Dosage/Usage

Merional is administered as intramuscular injection.

Induction of ovulation: the aim of the treatment is to bring a single Graaf follicle to maturation within a few days with the help of individually adjusted doses of Merional, subsequently to induce ovulation with an injection of human chorionic gonadotrophin (HCG).
The follicular maturation is assessed by hormonal controls and clinical examinations.
The hormonal controls include the assay of oestrogen levels in plasma.
The clinical examination includes the basal body temperature curve, ferning of the cervical mucus, determination of follicle size by ultrasonography.
The administration of Merional will be continued until the oestrogen rate and the follicle dimension indicate a pre–ovulatory phase:
Plasma oestrogens 300–800 pg (1.1–2.9 pMol)/ml
Average diameter of the dominant follicle 18–22 mm
Cervical score according to Insler ≥ 8 points out of 12.

These two treatment plans are followed:

Scheme 1: daily administration
The first injection of 1 vial of Merional 75 I.U. i.m. should be given on the 4th / 5th day following a spontaneous menstruation or an induced bleeding. The treatment at a daily dose of 1 vial of Merional 75 I.U. should last for 7 to 12 days maximum, or until an adequate follicular maturation is obtained. When used concomitantly with FSH, as a number of treatment protocols suggest, the dosage of Merional must be reduced accordingly. The result is assessed daily by ultrasonography and oestrogen control.
If the desired result is not obtained, the treatment can be discontinued or pursued with a dose of 2 vials/day (= 150 I.U. of Merional). Daily doses exceeding 150 I.U. can be administered only when the patient can be permanently kept under control.
The highest dose should not exceed 750 I.U. of HMG (10 vials of Merional 75 I.U. or 5 vials of Merional 150 I.U.) a day.
If, on the contrary, oestrogen plasma levels increase too fast (> 100% in 2–3 days), the dosage of Merional must be reduced.
24 to 48 hours after the last injection of Merional, a single dose of 5000 to 10000 I.U. of HCG i.m. can be administered, provided the clinical and biochemical results of the treatment show an appropriate but not excessive follicular stimulation.
Ovulation generally takes place 32 to 48 hours later. In case of failure, the administration of HCG can be repeated (see internal leaflet of any HCG preparation).

Scheme 2: administration every 2 days.
In this treatment plan, Merional is administered every other day. All other conditions (start, duration and monitoring of the treatment, administration of HCG) are the same as described in scheme 1.
The first of the two therapeutic schemes is the most commonly used.
The couple should be encouraged to have daily intercourse, beginning on the day prior to the administration of HCG, until ovulation is manifest. The rise of basal temperature should confirm it. If pregnancy does not occur in spite of ovulation, the treatment can be continued following the same scheme for at least 2 courses of treatment. A course of treatment at higher doses should be followed only in case of persistent failure and under a strict ultrasonographic and endocrinologic monitoring.

Induction of a multiple follicular growth, during a medically assisted conception program:
The dose of Merional has to be adapted to each patient according to the results given by the daily hormonal controls and by the echography.

1st phase: administer 150 to 300 I.U. of Merional i.m. daily, starting on the 3rd day of the cycle until a sufficient follicle growth is obtained. If, as suggested by a number of protocols, Merional is administered concomitantly with FSH, the dosage of the former must be reduced accordingly.

2nd phase: the ovulation is induced with an injection of 5000 to 10000 I.U. of HCG.

Administration
The solution should be reconstituted immediately before use, with the ampoule of solvent.
If higher doses have to be administered, it is possible to dissolve as many as 5 vials of Merional 75 I.U. (or as many as 2 vials of Merional 150 I.U.) in an ampoule of solvent.

Use restrictions

Contra–indications
The patients must be carefully selected, in order to rule out all cases whose pathology or particular conditions do not guarantee a successful therapy.
This is applicable in the following cases:
- pregnancy, lactation,
- premature menopause,
- known hypersensitivity to gonadotrophins, including HMG,
- primary ovarian failure (hypergonadotropic hypogonadism),
- sterility with impairment of normal follicular maturation (e.g. due to tubal or cervical factors), except patients who take part in a medically assisted conception program,
- ovarian cysts not due to polycystic ovary syndrome,
- gynecological bleeding of undetermined origin,
- hypergonadotropic ovarian insufficiency,
- hyperprolactinaemia,
- endocrinopathy of thyroidal or adrenal origin,
- ovarian, uterine or breast carcinoma,
- pituitary gland or hypothalamus tumor.

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Precautions
A treatment with gonadotrophins should be performed only by a physician with experience in the diagnosis and treatment of infertility problems. Any other possible cause of infertility should be excluded first (mechanical, immunological or andrological).
Moreover, access to the necessary equipment to perform clinical and endocrinologic controls must be guaranteed.
Before the treatment starts, thorough investigations must be carried out on the patient's and her partner's infertility, and any possible pregnancy contra-indication excluded. Both the patient and her partner must be informed that a treatment of infertility with gonadotrophins may increase the risk of ovarian hyperstimulation, multiple pregnancy and spontaneous abortions.

Ovarian hyperstimulation syndrome
In order to avoid this syndrome, the patient must be submitted to a clinical and endocrinologic examination at least every other day during the whole course of treatment and for 2 weeks after the end of it.
An excessive oestrogen reaction due to Merional does not generally cause any symptom of hyperstimulation. It is only after the administration of HCG that hyperstimulation may occur.
If the hormone dosage show an excessive oestrogen reaction or if clinical or sonographic signs of ovarian hyperstimulation should occur, the treatment with Merional must be immediately interrupted and HCG must not be injected (see «Dosage/Usage»).

The clinical signs of an ovarian hyperstimulation are:
mild hyperstimulation cases: abdominal pain or abdominal tension with ovarian enlargement;
in cases of moderate to severe hyperstimulation: sudden and marked ovarian hypertrophy, ascites with or without pleural effusion and hemodynamic disorders, rupture of ovarian cysts followed by peritonitis.
Symptoms of hyperstimulation generally appear 4 to 8 days after the administration of HCG.
For this reason the patient must be kept under control for at least 2 weeks after the last injection.
However, if symptoms similar to those of hyperstimulation should occur only 3 weeks or more after the end of the therapy, their origin should be ascribable to an imminent abortion or to an extra-uterine pregnancy.
In case of hyperstimulation of medium degree, a careful examination of the patient should be sufficient.
On the other hand, in case of ascites or severe complications, the patient must be hospitalized and submitted to an electrolythic and hemodynamic test.
In rare cases, an ovarian hyperstimulation syndrome with acute ovarian hypertrophy can be accompanied by the accumulation of fluids in the abdomen and thorax, as well as by more severe thromboembolic events.
The latter may occur in rare cases, independently from an ovarian hyperstimulation syndrome.
Women in superovulation treatment have a higher risk of developing a hyperstimulation, because of an excessive oestrogen response or a multifollicular development.
In certain patients, especially those with amenorrhea due to a Stein-Leventhal syndrome, the formation of ovarian cysts is possible. They cause abdominal pain of various intensity and require the discontinuation of the treatment.
In order to avoid the formation of cysts, the patient should undergo a gynecological examination every other day at the beginning of the treatment and daily starting from the 10th day of treatment.
The risks of hyperstimulation and formation of ovarian cysts are reduced if the recommended dosage and precautions are strictly followed.
According to Lunenfeld, a slight hyperstimulation occurs in less than 4% of cases, whereas a medium or severe hyperstimulation occurs in less than 1% of cases.

Multiple pregnancies
About 20% of pregnancies ensuing from a HMG/FSH treatment are multiple pregnancies the majority being twins.
After a medically assisted conception program, the risk of a multiple pregnancy increases proportionally with the number of implanted oocytes or embryos.

Abortions
The occurrence of spontaneous abortion is more frequent than in normal cases, but it is comparable to that occurring in women with infertility problems.
Ectopic pregnancies may occur in women with a history of tubal disorders.
However, the treatment does not increase the risk of foetus malformations in comparison with births issued from spontaneous pregnancies.

Pregnancy/Lactation
Pregnancy category: X.
There is evidence of a foetal risk, based on experience in humans or animals, therefore the administration of this drug to pregnant women is too risky, in comparison with the possible benefits. The drug is contra-indicated for pregnant women.
It is unknown whether HMG penetrates into milk and which effects it can have on breast-fed babies.
This drug is contra-indicated for lactating women.

Side effects
Irritation at the site of the injection, fever and arthralgies may be observed in rare cases.
Gastrointestinal symptoms, bloating, abdominal pain and breast tension may occur. A mild or moderate ovarian enlargement and formation of ovarian cysts are also possible. Severe ovarian hyperstimulation is rare (see «Precautions» and «Contra-indications»).
In rare cases, intravascular thrombosis and embolism, as well as peripheral and cerebral occlusions (e.g. pulmonary embolism, pulmonary infarction, cerebral vascular occlusion) were associated with a HMG/HCG treatment, even if ovarian hyperstimulation had not occurred.

Interactions
No clinically significant interactions have been reported with the use of Merional.
The concomitant treatment of Merional and clomiphene citrate can increase the follicular response, whereas the concomitant use of a hypophisary desensibilisation with a GnRH agonist may require the increase of the dosage of Merional in order to obtain an adequate ovarian response.

Overdosage
The effects of an overdosage with Merional are unknown. However, an ovarian hyperstimulation syndrome cannot be ruled out (see Precautions).

Other information
Storage
Ampoules of Merional must be stored at a temperature lower than 25°C.
Merional must not be used beyond the expiry date indicated on the package.
Once reconstituted with water for injection, Merional must be used immediately.

Package presentation
Vials 75 I.U. with the lyophilized substance + ampoules of solvent:
1 and 10.
Vials 150 I.U. with the lyophilized substance + ampoules of solvent:
1 and 10.

Distributor
IBSA – Institut Biochimique S.A., 6903 Lugano

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