Professional Information for Merional HG 75 IU

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

MERIONAL HG 75 IU powder for solution for injection and diluent

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder contains menotrophin (human menopausal gonadotropin, HMG) equivalent to 75 IU follicle stimulating hormone (FSH) activity and 75 IU luteinising hormone (LH) activity.

Menotrophin is produced from human urine.

Excipients with known effect:

Contains sugar (lactose monohydrate 10 mg/mL).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection and diluent.

Powder: White freeze-dried plug.

Diluent: Clear colourless and odourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MERIONAL HG is indicated for:

- Anovulation (including polycystic ovarian disease, PCOD) in women who have been unresponsive to treatment with clomifene citrate.
- Stimulation of multifollicular development in women undergoing assisted reproductive technologies (ART) such as *in vitro* fertilisation (IVF), gamete intrafallopian transfer (GIFT) and zygote intrafallopian transfer (ZIFT).

MERIONAL HG is indicated for use in adults only.

4.2 Posology and method of administration

Treatment with MERIONAL HG should be initiated under the supervision of a medical practitioner experienced in the treatment of fertility issues.

Posology

Women with anovulation (including PCOD):

The objective of treatment with MERIONAL HG is to develop a single mature Graafian follicle from which the ovum will be released after the administration of human chorionic gonadotrophin (hCG). MERIONAL HG 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.

MERIONAL HG 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 HG 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 hours after the last MERIONAL HG 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.

Women with anovulation resulting from severe LH and FSH deficiency:

In these women (hypogonadotrophic hypogonadism) the objective of 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 HG and is increased according to the patient's response. Should an increased dose of MERIONAL HG 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 – 10 000 IU of hCG should be administered 24 – 48 hours after the last MERIONAL HG injection. The patient should be recommended to have coitus on the hCG injection day and the following day. Alternatively, 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.

Women undergoing controlled ovarian stimulation for multiple follicular development prior to *in vitro* fertilisation or other assisted reproductive technologies:

A commonly used protocol for superovulation involves the administration of 150 – 225 IU of MERIONAL HG daily commencing on day 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 – 10 000 IU of hCG should be administered 24 – 48 hours after the last MERIONAL HG 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 HG 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 HG 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.

Method of administration

MERIONAL HG can be administered either intramuscularly (IM) or subcutaneously (SC).

MERIONAL HG should be inspected visually for particulate matter or discolouration prior to administration.

MERIONAL HG powder should be reconstituted prior to use with the diluent provided and administered immediately after reconstitution (see section 6.6).

4.3 Contraindications

MERIONAL HG should not be administered to women who have:

- Hypersensitivity to menotrophin or to any of the excipients of MERIONAL HG (see section 6.1).
- Tumours of the hypothalamus or pituitary gland.
- Ovarian enlargement or a cyst not due to polycystic ovarian disease.

- Gynaecological haemorrhages of unknown cause.
- Ovarian, uterine or mammary carcinoma.

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

- Primary ovarian failure.
- Malformation of sexual organs incompatible with pregnancy.
- Fibroid tumours of the uterus incompatible with pregnancy.

MERIONAL HG should not be used during pregnancy and lactation (see section 4.6).

There is no relevant use of MERIONAL HG in the paediatric population, therefore MERIONAL HG should not be administered to children.

4.4 Special warnings and precautions for use

MERIONAL HG is a potent gonadotrophin capable of causing mild to severe adverse reactions and its use should only be supervised by medical practitioners who are thoroughly experienced with infertility problems and their management. To minimise the risks of ovarian hyperstimulation syndrome (OHSS) or of multiple pregnancies, ultrasound scans as well as oestradiol measurements are mandatory during treatment.

Gonadotrophin therapy requires a certain time commitment by medical practitioners and supportive health care providers, as well as the availability of appropriate monitoring facilities. Safe and effective use of MERIONAL HG calls for monitoring of ovarian response with ultrasound alone or preferably in combination with measurement of serum oestradiol levels on a regular basis. There is considerable interpatient variability in response to MERIONAL HG administration with a poor response in some cases. The lowest effective dose in relation to the treatment objective should be used.

Treatment:

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, hyperprolactinaemia and pituitary or hypothalamic tumours, and appropriate specific treatment given.

Patients undergoing stimulation of follicular growth in ART procedures, may experience ovarian enlargement or develop hyperstimulation. Adherence to recommended dosage and regimen of MERIONAL HG administration and careful monitoring of therapy will minimise the incidence of such events. Accurate interpretation of the indices of follicular development and maturation requires a medical practitioner who is experienced in the interpretation of such data.

Ovarian hyperstimulation syndrome:

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 distension, severe ovarian enlargement, body mass gain, dyspnoea, oliguria and gastrointestinal symptoms including nausea, vomiting and diarrhoea. Clinical examination may reveal hypovolaemia, haemoconcentration, electrolyte imbalances, ascites, haemoperitoneum, pleural effusions, hydrothorax, acute pulmonary distress and thromboembolic events.

hCG used to trigger ovulation, may aggravate the ovarian hyperstimulation. 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 minimise the risk of OHSS or of multiple pregnancy, ultrasound scans as well as oestradiol measurements are mandatory. In anovulation the risk of OHSS and multiple pregnancy is increased by a serum oestradiol > 900 pg/mL (3 300 pmol/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 > 3 000 pg/mL (11 000 pmol/L) and 20 or more follicles of 12 mm or more in diameter. When the oestradiol level is > 5 500 pg/mL (20 200 pmol/L) and where there are 40 or more follicles in total, it may be necessary to withhold hCG administration.

Adherence to recommended MERIONAL HG dosage, regimen of administration and careful monitoring of therapy will minimise the incidence of ovarian hyperstimulation and multiple pregnancy.

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 HG the incidence of multiple pregnancies is increased as compared with natural conception. The majority of multiple

conceptions are twins. To minimise 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. The prevalence of ectopic pregnancy after IVF is reported to be 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 medicine regimens for infertility treatment.

Congenital malformations:

The prevalence of congenital malformations after ART is 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 women 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.

MERIONAL HG contains lactose monohydrate

Patients with rare hereditary problems of galactose intolerance total lactase deficiency or glucose-galactose malabsorption should not use MERIONAL HG.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use of MERIONAL HG with other medicines used to stimulate ovulation (e.g. hCG, clomifene citrate) may potentiate the follicular response.

Concurrent use of GnRH agonists to induce pituitary suppression may increase the dosage of MERIONAL HG needed to elicit an adequate ovarian response.

MERIONAL HG should not be administered as a mixture with other medicines in the same injection (see section 6.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

MERIONAL HG should not be administered during pregnancy (see section 4.3). In case of exposure during pregnancy clinical data are insufficient to exclude a teratogenic effect.

Breastfeeding

MERIONAL HG should not be used during breastfeeding (see section 4.3). During lactation the secretion of prolactin can entail a poor response to ovarian stimulation.

Fertility

MERIONAL HG is indicated for use in infertility (see section 4.1).

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, MERIONAL HG may cause dizziness, and this may affect the patient's ability to drive and use machines. Symptoms associated with OHSS may also impair the patient's ability to drive or to use machines.

4.8 Undesirable effects

Immune system disorders:

Less frequent: Systemic allergic reactions including symptoms such as erythema, rash or facial swelling.

Nervous system disorders:

Frequent: Headache.

Less frequent: Dizziness.

Vascular disorders:

Less frequent: Thromboembolism.

Gastrointestinal disorders:

Frequent: Abdominal pain, nausea, vomiting, diarrhoea, abdominal cramps, bloating.

Skin and subcutaneous tissue disorders:

Frequent: Acne.

Reproductive system and breast disorders:

Frequent: Ovarian cysts, OHSS (for symptoms associated with OHSS see section 4.4 – Ovarian hyperstimulation).

Less frequent: Ovarian torsion.

General disorders and administration site conditions:

Frequent: Weight gain and injection site reaction including symptoms such as pain, redness, bruising, swelling and/or irritation at the site of injection.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of MERIONAL HG is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety App (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA's website.

4.9 Overdose

For symptoms associated with OHSS see section 4.4 – Ovarian hyperstimulation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class:

Powder: A 21.10 Trophic hormones

Diluent: A 32.16 Others

Pharmacotherapeutic group: Gonadotrophins.

ATC code: G03GA02

Menotrophin is a human menopausal gonadotrophin (HMG) obtained from the urine of post-menopausal women. Menotrophin contains both follicle stimulating hormone activity and luteinising hormone activity.

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

5.2 Pharmacokinetic properties

Human menopausal gonadotrophin 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. FSH peak concentrations reached 6,5 ± 2,1 IU/L with an AUC_{0-t} of 438,0 ± 124,0 IU x h/L after IM administration. After SC administration, C_{max} reached 7,5 ± 2,8 IU/L with an

AUC_{0-t} of 485,0 ± 93,5 IU x h/L. After a single injection of 300 IU menotrophin, 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Lactose monohydrate.

Diluent:

0,9 % *m/v* sodium chloride

Water for injection.

6.2 Incompatibilities

MERIONAL HG powder should not be mixed with other medicines.

6.3 Shelf life

24 months.

MERIONAL HG powder should be reconstituted prior to use and administered immediately after

reconstitution.

The reconstituted solution is for single use only.

6.4 Special precautions for storage

Store at or below 25 °C.

Do not freeze.

Store in the original container, protected from light.

Discard any unused portion.

6.5 Nature and contents of container

MERIONAL HG 75 IU (vial and ampoule):

Powder: One 4 mL Type I clear glass vial, fitted with a grey bromobutyl rubber stopper and an aluminium seal with a dark green coloured flip-off cap.

Diluent (ampoule): One 1 mL Type I clear glass ampoule, coded with yellow and blue coloured bands and a red dot.

Pack size: Each pack contains either 1 vial and 1 ampoule or 10 vials and 10 ampoules in an outer carton.

OR

MERIONAL HG 75 IU (vial and pre-filled syringe):

Powder: One 4 mL Type I clear glass vial, fitted with a grey bromobutyl rubber stopper and an aluminium seal with a dark green coloured flip-off cap.

Diluent (pre-filled syringe): One Type I colourless glass syringe, with a grey tip cap at one end and a siliconised plunger stopper at the other end.

Pack size: Each pack contains 1 vial, 1 pre-filled syringe with diluent and 2 needles (1 needle for reconstitution/intramuscular injection [0,8 x 40 mm] and 1 needle for subcutaneous injection [0,4 x 12 mm]) placed in a plastic tray packaged in an outer carton.

6.6 Special precautions for disposal and other handling

MERIONAL HG powder should be reconstituted prior to use with the diluent provided and administered immediately after reconstitution.

The reconstituted solution is a clear colourless solution free from any foreign particles.

The solution should be prepared using aseptic technique to minimise contamination. The reconstituted solution is for single use only.

Instructions for reconstitution of vial and ampoule with diluent:

1. Carefully break the top off the diluent ampoule by snapping it where the red dot is. Aseptically withdraw 1 mL of diluent. Inspect the diluent visually for particulate matter or discolouration.
2. Remove the dark green coloured flip-off cap from the vial.
3. Through the rubber stopper, slowly inject the diluent solution down the inside of the vial into the white powder.
4. The white powder dissolves immediately without the need to shake the vial.
5. Slowly withdraw the solution into the syringe.

Instructions for reconstitution of vial and pre-filled syringe with diluent:

1. Remove the cap from the pre-filled syringe and apply the reconstitution needle (longer needle).
2. Remove the dark green coloured flip-off cap from the vial.
3. Take the pre-filled syringe and slowly inject its contents into the powder vial through the rubber stopper.
4. Roll the vial gently several times (**do not shake**) until the powder has completely dissolved, taking care to avoid the formation of foam.
5. Once the powder has completely dissolved withdraw the solution into the syringe again. The solution must be clear and colourless.

Reconstituting more than one vial:

In order to avoid injection of large volumes up to 5 vials of MERIONAL HG may be dissolved in 1 mL diluent. To provide the prescribed dose in a single 1 mL injection, slowly inject the solution already in the syringe into the next vial, repeating steps 3 – 5 above. 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 HG (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 diluent then gently and slowly roll the vial between the fingers until the powder is completely dissolved.

During reconstitution avoid shaking the vial as this will cause foaming. If excessive foaming does occur discard vial and start again.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Delfran Pharmaceuticals (Pty) Ltd

Unit 7 Diamond Park, 70 Jacaranda Street

Hennopspark

Centurion

0157

8. REGISTRATION NUMBER

48/21.10/0402

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 March 2019

10. DATE OF REVISION OF THE TEXT

25 August 2025