

**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.

22

23 **4. CLINICAL PARTICULARS**24 **4.1 Therapeutic indications**

25 MERIONAL HG is indicated for:

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

31 MERIONAL HG is indicated for use in adults only.

32

33 **4.2 Posology and method of administration**

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

36

37 **Posology**38 **Women with anovulation (including PCOD):**

39 The objective of treatment with MERIONAL HG is to develop a single mature Graafian follicle from  
40 which the ovum will be released after the administration of human chorionic gonadotrophin (hCG).  
41 MERIONAL HG may be given as a course of daily injections. In menstruating patients, treatment  
42 should be started within the first seven days of the menstrual cycle.

43

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.

94

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

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

104

#### 105 **Method of administration**

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

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

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

111

#### 112 **4.3 Contraindications**

113 MERIONAL HG should not be administered to women who have:

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

Signed: 

25 August 2025

Page 5 of 18

117 • Gynaecological haemorrhages of unknown cause.

118 • Ovarian, uterine or mammary carcinoma.

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

120 • Primary ovarian failure.

121 • Malformation of sexual organs incompatible with pregnancy.

122 • Fibroid tumours of the uterus incompatible with pregnancy.

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

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

126

#### 127 **4.4 Special warnings and precautions for use**

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

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

140

Signed: 

25 August 2025

Page 6 of 18

**141 Treatment:**

142 Before starting treatment, the couple's infertility should be assessed as appropriate and putative  
143 contraindications for pregnancy evaluated. In particular, patients should be evaluated for  
144 hypothyroidism, adrenocortical deficiency, hyperprolactinaemia and pituitary or hypothalamic  
145 tumours, and appropriate specific treatment given.

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

151

**152 Ovarian hyperstimulation syndrome:**

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

157 The following symptoms may be observed in severe cases of OHSS: abdominal pain, abdominal  
158 distension, severe ovarian enlargement, body mass gain, dyspnoea, oliguria and gastrointestinal  
159 symptoms including nausea, vomiting and diarrhoea. Clinical examination may reveal  
160 hypovolaemia, haemoconcentration, electrolyte imbalances, ascites, haemoperitoneum, pleural  
161 effusions, hydrothorax, acute pulmonary distress and thromboembolic events.

162 hCG used to trigger ovulation, may aggravate the ovarian hyperstimulation. Therefore, in cases of  
163 OHSS it is prudent to withhold hCG and to advise the patient to refrain from coitus or to use barrier  
164 methods for at least four days. OHSS may progress rapidly (within 24 hours to several days) to

165 become a serious medical event, therefore patients should be followed for at least two weeks after  
166 hCG administration.

167 To minimise the risk of OHSS or of multiple pregnancy, ultrasound scans as well as oestradiol  
168 measurements are mandatory. In anovulation the risk of OHSS and multiple pregnancy is  
169 increased by a serum oestradiol > 900 pg/mL (3 300 pmol/L) and more than 3 follicles of 14 mm or  
170 more in diameter. In ART there is an increased risk of OHSS with a serum oestradiol >  
171 3 000 pg/mL (11 000 pmol/L) and 20 or more follicles of 12 mm or more in diameter. When the  
172 oestradiol level is > 5 500 pg/mL (20 200 pmol/L) and where there are 40 or more follicles in total, it  
173 may be necessary to withhold hCG administration.

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

177 In ART, aspiration of all follicles prior to ovulation may reduce the occurrence of hyperstimulation.  
178 OHSS may be more severe and more protracted if pregnancy occurs. Most often OHSS occurs  
179 after hormonal treatment has been discontinued and reaches its maximum at about 7 – 10 days  
180 following treatment. Usually, OHSS resolves spontaneously with the onset of menses.

181 If severe OHSS occurs, gonadotrophin treatment should be stopped if still ongoing, the patient  
182 hospitalised and specific therapy for OHSS started. This syndrome occurs with higher incidence in  
183 patients with polycystic ovarian disease.

184

185 **Multiple pregnancy:**

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

188 In patients undergoing ovulation induction with MERIONAL HG the incidence of multiple  
189 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.

## 213 **Thromboembolic events:**

214 In women with generally recognised risk factors for thromboembolic events, such as personal or  
215 family history or significant obesity, treatment with gonadotrophins may further increase the risk.

216

## 217 **MERIONAL HG contains lactose monohydrate**

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

220

## 221 **4.5 Interaction with other medicines and other forms of interaction**

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

224

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

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

229

## 230 **4.6 Fertility, pregnancy and lactation**

### 231 **Pregnancy**

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

234

### 235 **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.

259

260 **Gastrointestinal disorders:**261 *Frequent:* Abdominal pain, nausea, vomiting, diarrhoea, abdominal cramps, bloating.

262

263 **Skin and subcutaneous tissue disorders:**264 *Frequent:* Acne.

265

266 **Reproductive system and breast disorders:**267 *Frequent:* Ovarian cysts, OHSS (for symptoms associated with OHSS see section 4.4  
268 – Ovarian hyperstimulation).269 *Less frequent:* Ovarian torsion.

270

271 **General disorders and administration site conditions:**272 *Frequent:* Weight gain and injection site reaction including symptoms such as pain,  
273 redness, bruising, swelling and/or irritation at the site of injection.

274

275 ***Reporting of suspected adverse reactions***276 Reporting suspected adverse reactions after authorisation of MERIONAL HG is important. It allows  
277 continued monitoring of the benefit/risk balance of the medicine. Health care providers are  
278 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety App  
279 (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA's website.

280

281 **4.9 Overdose**

Signed:



25 August 2025

Page 12 of 18

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

283

## 284 **5. PHARMACOLOGICAL PROPERTIES**

### 285 **5.1 Pharmacodynamic properties**

286 Category and class:

287 Powder: A 21.10 Trophic hormones

288 Diluent: A 32.16 Others

289 Pharmacotherapeutic group: Gonadotrophins.

290 ATC code: G03GA02

291

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

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

297

### 298 **5.2 Pharmacokinetic properties**

299 Human menopausal gonadotrophin is not effective when taken orally and is injected either  
300 intramuscularly or subcutaneously. The biological effectiveness of HMG is mainly due to its FSH  
301 content.

302 The pharmacokinetics of HMG following intramuscular or subcutaneous administration show great  
303 individual variation. FSH peak concentrations reached  $6,5 \pm 2,1$  IU/L with an  $AUC_{0-t}$  of  $438,0 \pm$   
304  $124,0$  IU x h/L after IM administration. After SC administration,  $C_{max}$  reached  $7,5 \pm 2,8$  IU/L with an

Signed: 

25 August 2025

Page 13 of 18

305 AUC<sub>0-t</sub> of 485,0 ± 93,5 IU x h/L. After a single injection of 300 IU menotrophin, the maximum serum  
306 level of FSH is reached approximately 19 hours after intramuscular injection and 22 hours after  
307 subcutaneous injection.

308 After that, the serum level decreases by a half-life of approximately 45 hours following  
309 intramuscular administration and 40 hours following subcutaneous administration.

310 Excretion of HMG, following administration, is predominantly renal.

311

## 312 **6. PHARMACEUTICAL PARTICULARS**

### 313 **6.1 List of excipients**

#### 314 ***Powder:***

315 Lactose monohydrate.

316

#### 317 ***Diluent:***

318 0,9 % *m/v* sodium chloride

319 Water for injection.

320

### 321 **6.2 Incompatibilities**

322 MERIONAL HG powder should not be mixed with other medicines.

323

### 324 **6.3 Shelf life**

325 24 months.

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

Signed: 

25 August 2025

Page 14 of 18

327 reconstitution.

328 The reconstituted solution is for single use only.

329

#### 330 **6.4 Special precautions for storage**

331 Store at or below 25 °C.

332 Do not freeze.

333 Store in the original container, protected from light.

334 Discard any unused portion.

335

#### 336 **6.5 Nature and contents of container**

337 MERIONAL HG 75 IU (vial and ampoule):

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

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

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

344 **OR**

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

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

Signed: 

25 August 2025

Page 15 of 18

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

350 Pack size: Each pack contains 1 vial, 1 pre-filled syringe with diluent and 2 needles (1 needle for  
351 reconstitution/intramuscular injection [0,8 x 40 mm] and 1 needle for subcutaneous injection [0,4 x  
352 12 mm]) placed in a plastic tray packaged in an outer carton.

353

## 354 **6.6 Special precautions for disposal and other handling**

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

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

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

360

### 361 **Instructions for reconstitution of vial and ampoule with diluent:**

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

369

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



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

379

380 **Reconstituting more than one vial:**

381 In order to avoid injection of large volumes up to 5 vials of MERIONAL HG may be dissolved in  
382 1 mL diluent. To provide the prescribed dose in a single 1 mL injection, slowly inject the solution  
383 already in the syringe into the next vial, repeating steps 3 – 5 above. The minimum number of vials  
384 needed to achieve the intended dose should be used wherever possible to minimise the number of  
385 reconstitution operations.

386 Care must be taken when reconstituting more than 1 vial of MERIONAL HG (in 1 mL diluent) so as  
387 to avoid foaming of the reconstituted solution. If some of the white powder is not in contact with the  
388 diluent then gently and slowly roll the vial between the fingers until the powder is completely  
389 dissolved.

390

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

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Signed: 

25 August 2025

Page 17 of 18

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

395

396 **7. HOLDER OF CERTIFICATE OF REGISTRATION**

397 Delfran Pharmaceuticals (Pty) Ltd

398 Unit 7 Diamond Park, 70 Jacaranda Street

399 Hennopspark

400 Centurion

401 0157

402

403 **8. REGISTRATION NUMBER**

404 48/21.10/0402

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406 **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

407 29 March 2019

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409 **10. DATE OF REVISION OF THE TEXT**

410 25 August 2025

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Signed: 

25 August 2025

Page 18 of 18