Merional sc 75 IU & 150 IU, powder and solvent for solution for injection

(menotrophins)

PLs 21039/0016 & 0017

UKPAR

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The MHRA granted IBSA Farmaceutici Italia Srl a Marketing Authorisation for the medicinal product Merional sc 75 IU/150 IU, powder and solvent for solution for injection (PL 21039/0016 & 0017) on 2nd August 2011. This medicine is subject to restricted medical prescription and is indicated for the treatment of anovulation (including polycystic ovarian disease, PCOD) in women who have been unresponsive to treatment with clomiphene citrate and 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/150 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 contains menotrophin (human menopausal gonadotrophin) as an active ingredient and is a blend of follicle stimulating hormone (FSH) and luteinizing hormone (LH) to the ratio of 1:1 of FSH:LH activity plus small amounts of human chorionic gonadotrophin (hCG). Human chorionic gonadotrophin is added to supplement the LH activity. In women, LH stimulates oestrogen and progesterone production from the ovary. In men, LH stimulates testosterone production from the interstitial cells of the testes (Leydig cells).

Merional sc is a sterile, lyophilised powder of highly purified menotrophin (human menopausal gonadotrophin) intended for injection after reconstitution with sterile 0.9% sodium chloride solution. The formulation of the lyophilised drug product contains lactose monohydrate as the sole excipient.

A critical review of the clinical and pharmaceutical data presented to the MHRA demonstrated that Merional is effective in the treatment of anovulation.
Merional sc 75 IU & 150 IU, powder and solvent for solution for injection
(menotrophins)
PLs 21039/0016 & 0017

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of data on quality, safety and efficacy the UK granted a Marketing Authorisation to IBSA Farmaceutici Italia Srl for the medicinal product Merional sc 75 IU/150 IU, powder and solvent for solution for injection (PL 21039/0016 & 0017) on 2nd August 2011. This product is a restricted prescription only medicine.

This application was submitted as an abridged complex national application under Article 8(3) of Directive 2001/83/EC as amended. This application has been submitted as a line extension to introduce an alternative subcutaneous (sc) route of administration to the existing intra-muscular (im) route. The national marketing authorization in the UK was first granted on 21st August 2002 (PL 21039/0010 & 0011), and has since been approved on a national basis in approximately 30 countries.

Merional is indicated for the treatment of anovulation (including polycystic ovarian disease, PCOD) in women who have been unresponsive to treatment with chlomiphene citrate and 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/150 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 contains menotrophin (human menopausal gonadotrophin) as an active ingredient. By its composite description it is a blend of follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the urine of post-menopausal women plus small amounts of human chorionic gonadotrophin (hCG) purified from urine of pregnant women. The hormones are blended to achieve the 1:1 ratio of FSH:LH activity. Human chorionic gonadotrophin is added to supplement the LH activity.

Merional was granted a licence on 2nd August 2011.
QUALITY ASSESSMENT

I. REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORISATION

No changes are proposed for the Drug Substance. The drug product manufacturer IBSA is responsible for primary and secondary packaging. The MAH has provided details of the batch release site. The applicant has provided current manufacturing authorisations and GMP inspection certificates for the drug product manufacturers.

No changes are proposed to the current manufacturing sites and consequently no inspections are currently required.

II. INTRODUCTION

Merional is a lyophilised powder of highly purified urinary-derived menotrophin. Menotrophins are used in the treatment of female and male infertility. The national marketing authorization in the UK was first granted on 21st August 2002 (PL 21039/0010 & 0011, for 75 and 150 IU strengths respectively). The product has since been approved on a national basis in approximately 30 countries.

After discussion with the MHRA regarding the legal classification, it was agreed that this application could be presented as an abridged application according to Article 8(3). The submission package contains administrative, quality and clinical data but no new pre-clinical data is required. The proposed MA is for a presentation which has the same qualitative and quantitative composition in the drug product to the currently approved licence for intramuscular injection.

The applicant has referred to the currently approved quality dossiers for PL 21039/0010−0011, including subsequent variations after the initial approval. It can therefore been accepted that no further assessment is required for Module 3.2.S. It is noted that, due to the date of the initial approval, the Drug Substance dossier is not fully compliant with the CTD format. A new Module 3.2.P CTD conversion has been provided for both the Merional drug product and for 0.9% sodium chloride solvent for reconstitution.

This assessment will cover only the areas of the CTD affected by the introduction of these line extensions. Assessment of the two strengths, 75 and 150 IU will be presented in one assessment report as the data presented in most aspects of the quality dossier overlaps to a great extent.

III. DRUG SUBSTANCE

No new information or assessment is required since the drug substance is unchanged.

The applicant has confirmed that the active ingredient of Merional sc 75 IU and 150 IU powder and solvent for solution for injection is menotrophin (human menopausal gonadotrophin; HMG). By its composite description it is a blend of follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the urine of post-menopausal women plus small amounts of HCG purified from urine of pregnant women. The hormones are blended to achieve the 1:1 ratio of FSH: LH activity. Human chorionic gonadotrophin (hCG) is added to supplement the LH activity.

There are no changes proposed to the qualitative or quantitative composition of the drug substance and the applicant refers to the data in the approved dossier for PL 21039/0010–0011.
The applicant has also confirmed that the identical starting material form the same source is used. The starting material is pooled donated urine collected from healthy women. The crude material is then transported to the manufacturing sites for downstream fractionation and purification.

The applicant has also confirmed that no changes are proposed to the Drug Substance Specifications. The Drug Substance will continue to be stored in the same immediate container and stored under the same conditions as the current product.

This assessment has not revisited this data and the Drug Substance can be approved for use in the subcutaneous product on the basis that it has already been deemed acceptable.

IV. DRUG PRODUCT

IV.1 Description and composition of the drug product

Merional sc is a sterile, lyophilised powder of highly purified menotrophin (human menopausal gonadotrophin) intended for injection after reconstitution with sterile 0.9% sodium chloride solution. Both strengths are presented as a lyophilised product which is qualitatively and quantitatively identical in formulation to that of the previously approved Merional products containing the excipient lactose monohydrate.

IV.2 Pharmaceutical development

The pharmaceutical development of the proposed formulation of Merional has been previously evaluated in the original dossier. The replacement of mannitol with excipient lactose monohydrate was utilised to optimise the formulation and water for injection was replaced with an isotonic, sterile 0.9% sodium chloride solution. These changes were all evaluated and approved by means of appropriate variation procedures. The company have not proposed any further changes in this submission.

IV.3 Manufacture

The manufacturing process also remains unchanged by this submission. Since grant of the original MA, a new manufacturing site has been introduced by means of Type II Variation.

The applicant has provided the appropriate descriptions and flow chart along with in-process controls which confirm that the intended process is unchanged for the previously approved products.

IV.4 Control of excipients

Lactose, water for injection and nitrogen all comply with the relevant Ph.Eur monographs.

IV.5 Control of finished product

The applicant has confirmed that the Finished Product Specification remains unchanged. The currently approved analytical procedures and the validation of methods apply.

The applicant has referred to batch analysis submitted for previous applications and three batches of the 75 IU and one of the 150 IU strength. Additional batch release data for 150 IU strength was requested in line with an outstanding FUM for this strength. Satisfactory batch release data for two lots of 150 IU product was provided.
IV.6 Reference standards or materials

No changes are proposed to that presented for PL 21039/0010.

IV.7 Container closure system

The lyophilised powder is presented within a 5ml, colourless type I glass vial with a rubber stopper. Both have been confirmed as conforming to the Ph.Eur. The closure is secured with an aluminium collared cap. No changes are proposed to the specification for the primary packaging and are consequently considered acceptable.

IV.8 Stability

No changes are proposed to the storage conditions (Do not store above 25°C) or the shelf-life of 24 months, as previously submitted for PL 21039/0010. Adequate real time and accelerated stability data for the 75 IU/ml and 150 IU/ml strengths have been provided. Taken together with a commitment to complete ongoing stability studies, this can be considered sufficient for approval.

The applicant has provided sufficient data for approval of the proposed shelf-life and storage conditions based on the currently approved Merional MA. The applicant has also provided satisfactory clarification of the current status of stability data for product manufactured at the current site and using the current process. A letter of commitment has been provided which includes an undertaking to provide a full stability update with the intended Type II variation to include s/c in the original Merional PLs.

IV. DILUENT

The proposed diluent, sodium chloride 0.9% solution for injection is identical to that already approved for PL 21039/0010. It, and its components all conform to the appropriate Ph.Eur monographs.

Details of the diluent manufacturer are provided, comprising copies of the appropriate manufacturing authorisation and GMP certificate issued by the relevant national competent authority. A description and flow chart of the manufacturing process and supporting validation is provided in the quality dossier for the solvent for injection. The product is filled into colourless, Ph.Eur. type I glass ampoules, with a fill volume of 1 ml. The specification tests and limits are unchanged and are acceptable.

V. APPENDICES

A.1 Facilities and equipment

Appropriate details have been provided which confirm that no changes have been made to the previously approved facilities and equipment.

A.2 Adventitious agents safety evaluation

Excipients of human or animal origin

The product contains lactose as an excipient, derived from bovine milk. The applicant refers to EMEA/410/01, current revision, which states that milk is unlikely to present any risk of TSE contamination. The lactose used is identical to that previously approved and no further assessment is considered necessary.
A.3 Novel excipients
N/A

VI. REGIONAL INFORMATION
N/A

VII. ASSESSOR’S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET

SmPC and PIL
These are acceptable.

VIII. ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY

The applicant has confirmed that the proposed product is identical in all quality aspects to the currently approved product. The application is approvable.

The following post-approval commitments have been agreed:

1. The labels submitted are not intended for marketing and will be revised to include clearly distinguishing features to prevent confusion with Merional PL 21039/0010 and 0011 should marketing ever be intended.

2. Post-approval stability commitments have been provided. It is acceptable that they are reported in the form of further stability data as part of the submission for the Type II variation to add the s/c route of administration to PL 21039/0010 and 0011.

3. The company have agreed to review the use of ampoules in the reconstitution solution for presentation of product intended for self-administration by patients at home. They have committed to review this at the time of submission of the Type II variations to add the sc route to PL 21039/0010 and 0011.
I. INTRODUCTION

I.1 Type of application and aspects on development

These are national applications for Merional sc powder and solvent for solution for injection 75 IU and 150 IU submitted as line extensions to the already licensed Merional powder and solvent for solution for injection 75 IU and 150 IU under Article 8 (3) to introduce the subcutaneous (sc) route of administration to the existing intra-muscular (im) route.

The active substance is a lyophilised powder of highly purified urinary-derived menotrophin. Merional powder and solvent for solution for injection 75 IU and 150 IU was first granted a National Marketing Authorization on 21/08/2002 (PL 21039/0010−0011) for dosing via the im route of administration. The product has since been approved on a national basis in approximately 30 countries.

The proposed indication is:

- **Anovulation (including polycystic ovarian disease, PCOD) in women who have been unresponsive to treatment with chlomiphene 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 sc 75 IU/150 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.**

II. PHARMACOLOGY/PHARMACOKINETICS/TOXICOLOGY

Menotrophin is a well-established active substance and there is a wealth of clinical data available following the use of the existing 75 IU and 150 IU im preparations. The proposed drug substance is identical to that already licensed and as such no new pharmacology or pharmacokinetic studies have been submitted in support of this application and none are required.

The proposed MA is for a presentation which has the same qualitative and quantitative composition for the drug product as the currently approved licence and the applicant has referred to the currently approved dossier.

No non-clinical local tolerance investigations have been conducted to support the different route of administration. This is acceptable given that the proposed sc preparation is licensed in other member states and there is a wealth of clinical data available which obviates the need for further non-clinical studies.

The non-clinical expert report is brief but adequate for this particular product, citing 10 papers up to 2009.

The non-clinical sections of the SPC are identical to those of the already licensed product and are therefore acceptable.
II.2 Ecotoxicity/environmental risk assessment

An environmental risk assessment has been submitted by the applicant.

Given that the indications are identical for this product compared with that already licensed it could be argued that the use of this product will simply replace the use of the existing product and that no increased environmental exposure is expected. As such it is considered that there is no need for an updated environmental risk assessment for this particular product. This is acceptable.

III. ASSESSOR’S OVERALL CONCLUSIONS

Menotrophin is an established active substance and there is a wealth of clinical data available. As a line extension application, no non-clinical studies are required and none have been provided. Clinical data are available which obviates the need for bridging studies to assess local tolerance.

With regard to the environmental risk assessment, it is taken into account that this product is a line extension to an already licensed product for identical indications. As such it is anticipated that the use of this product will replace the use of the existing product and that no increased environmental exposure to the active substances is expected. Therefore there is no need for an amended environmental risk assessment for this particular product.

The non-clinical sections of the SmPC are identical to those of the licensed product and are acceptable.

The granting of a Marketing Authorisation to this product is recommended from a non-clinical perspective.
I. INTRODUCTION

I.1 Type of application and regulatory background
This is a national abridged application for Merional which seeks to add the subcutaneous route of administration to the posology.

Merional (menotrophin) is a purified preparation of gonadotrophins extracted from the urine of post-menopausal women and belongs to the WHO therapeutic group G03GA02, gonadotrophins. Merional was originally licensed in the UK in February 2002 and is registered and commercially available in 15 countries worldwide. Where Merional is licensed, it is registered for s.c. administration in all but three of these countries including EU member states and other EEA countries e.g. Switzerland. Registration outside of EU/EEA is extensive.

1.2 Indication
The registered therapeutic indications for Merional involve the treatment of female and male infertility in the following groups of patients:

- 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/150 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.

1.3 Clinical background
Gonadotrophins (LH, FSH, CG) are natural glycoprotein hormones required for ovulation, spermatogenesis and the bio-synthesis of the sex steroids. Currently available human gonadotrophin preparations are derived from female urine obtained either after menopause (human menopausal gonadotrophin, hMG) or during the first trimester of pregnancy (human chorionic gonadotrophin, hCG). The standard hMG preparations contain follicle stimulating hormone (FSH) and luteinizing hormone (LH) bioactivity in a ratio of approximately 1:1, though some preparations are available in which the ratio is 3:1.

These preparations are intended for the treatment of female and male fertility disorders resulting from inadequate gonadotrophin stimulation of the gonads as well as for controlled ovarian hyperstimulation in medically assisted reproduction programmes, such as in-vitro fertilisation (IVF). In the woman, the hMG stimulates the growth and maturation of the follicles which favour the oestrogens production. Thus the endometrium is induced to proliferate and the implantation and nestling of a fertile ovum is then possible. Clinical experience indicates the occurrence of ovulation in approximately 90% of appropriately selected patients. In man, hMG acts particularly on the seminiferous tubules stimulating, in the Sertoli cells, the production of the androgen fixing proteins. In this way spermatogenesis is stimulated. Urinary gonadotrophins have been used for more than 30 years in the treatment of female and male infertility and most of them are indicated for im use.

Until recently, it was believed that urinary gonadotrophins could not be injected sc, since the administration of these preparations with relatively high amounts of impurities via this route may induce undesirable local adverse reactions. Although data have been presented indicative of an allergic potential of sc injected urinary gonadotrophins in a non-homologous animal model, clinical studies performed so far have indicated that the risk of allergic reactions is minimal and they support
the safe administration of urinary gonadotrophins via the sc route. Thus, the bioequivalence issue of sc and im administration of gonadotrophins is important in clinical decision making when choosing an administration route for these preparations.

In support of this application, a pharmacokinetic study, PK003 and a single therapeutic equivalence study, HMG06 administered by the sc and im routes have been submitted.

GCP aspects
The applicant has stated that the study was performed in accordance with the relevant guidelines of the Declaration of Helsinki.

II. CLINICAL STUDIES
II.1 Pharmacokinetic study
Title of the study:
Comparative pharmacokinetic study comparing sc to im administration of hMG in female healthy volunteers.

Objectives:
The aim of the present study was to compare the kinetic profile of hMG (FSH/LH 1:1) administered by sc route vs. im route when given as Merional injectable ampoules in healthy female volunteers.

Study design
Single centre, randomised, cross-over study.

Clinical phase: I

Number of subjects:
18 female healthy volunteers, aged 20–39 years and under oral contraceptive treatment.

Study medication:
Merional 150 IU
Active constituent: human menopausal gonadotrophin (hMG) 150 IU
Chemical name: FSH/LH 1:1

Treatment A: Merional 300 IU for sc administration (test)
Treatment B: Merional 300 IU for im administration (reference)

Inclusion Criteria:
Volunteers had to fulfil all of these criteria to be enrolled in the study:
Physical examination
> Sex: females
> Age: 18–40 years old
> Body weight: within ± 20 % of normal BW according to sex, age and build
> Pregnancy: No pregnant or lactating women

Vital signs: normal values of BP (100–139 mm Hg systolic and 50–89 mm Hg diastolic) and of HR (50–90 bpm), measured after 5 min of rest in the supine position.
ECG (12 leads): no clinically relevant abnormalities.
Physical findings: no clinically important abnormal physical findings which could interfere with the objectives of the study.
Laboratory analyses: no clinically relevant abnormal laboratory values indicative of physical illness
Medical history

**Contraception:** use of combined oral contraceptives during at least 3 months prior to the study

**Menstrual cycle:** history of normal cycle before the use of oral contraceptives

**Allergy:** no ascertained or presumptive hypersensitivity to the active principle and/or formulation ingredients; no history of anaphylaxis to drugs or allergic reactions in general, which the investigator considers may affect the outcome of the study.

**Diseases:** No history of endocrine abnormalities such as hyperprolactinaemia or uncontrolled thyroid and adrenal dysfunction; no polycystic ovary disease, ovarian cysts, primary ovarian failure, early menopause or abnormal bleeding of undetermined origin (contraindications for the use of combined oral contraceptives or gonadotrophins).

No relevant history of renal, hepatic, cardiovascular, respiratory diseases that may interfere with the aim of the study, or neoplasias.

**Medications:** no treatment with gonadotrophin preparations within a period of 6 months prior to screening; no other medications during 2 weeks before the start of the study, which the investigator considers may affect the validity of the study.

**Investigative drug trials:** no participation in the evaluation of any drug within 3 months prior to screening.

**Blood donation** no blood donation during the 3 months prior to this study.

**Drug, alcohol, tobacco:** no history of drug, alcohol or tobacco abuse (<40 g/day alcohol; <10 cigarettes/day).

**Full comprehension:** ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the investigator and to comply with the requirements of the entire study.

**Informed consent:** willing to give written informed consent to be signed prior to inclusion in the study.

**Blood samples collection**

Venous blood samples (8 mL) were collected on day 20+/− in order to assess compliance with the oral contraceptive treatment. Venous blood samples (8 mL) were collected on days 22, 23, 24, 25, 26, 28, 30 and on days 36, 37, 38, 39, 40, 42, 44 from a vein of the forearm at the following times after the drug administration: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30, 36, 48, 72, 96, 144 and 192 h.

**STUDY END POINTS**

**Primary end point**

Comparative pharmacokinetics of 300 IU hMG sc vs. im administration assessed as FSH AUC, $C_{\text{max}}$ and $t_{\text{max}}$.

**Secondary end point**

Comparative pharmacokinetic of 300 IU hMG sc vs. im administration assessed as LH AUC, $C_{\text{max}}$ and $t_{\text{max}}$.

Main pharmacokinetic parameters of FSH and LH.

**DATA ANALYSIS**

**PK non-compartmental analysis**

A descriptive pharmacokinetics was presented. The results were displayed and summarised by tables and plots. Mean curves were plotted indicating inter-subjects variability (SD around sampling times). The pharmacokinetic parameters measured and/or calculated for both FSH and LH were: $C_{\text{max}}$, $t_{\text{max}}$, $t_{1/2}$, AUC$_I$, AUC$_{\infty}$ and MRT.

AUC was calculated after baseline subtraction.
Statistical comparison
Analysis of variance (ANOVA) was performed on log-transformed data for all calculated PK parameters.
According to the current European Guidelines, the following statistical comparisons of the relevant pharmacokinetic parameters obtained for the two pharmaceutical forms were made:
The values of AUC and C max calculated for FSH and LH after sc and im administration were compared by the analysis of variance (ANOVA) for a cross-over design (log transformed data) at the level of significance p<0.05.
The 90% confidence interval of the ratio of the values obtained for the test and reference formulation was calculated.
The acceptance criterion for bioequivalence was the following: the 90% confidence interval of the ratio of the mean test to the mean reference values had to be included within the range 0.80–1.25. As a confirmation of the bioequivalence criteria, a two one-sided t-test was carried out for C max and AUC. Left and right tails were calculated for the lower and upper limits.
The value t max after sc and im administration was compared by the non-parametric Friedman test (non-transformed data).

Results

Study population
Eighteen healthy female volunteers were enrolled in this study. 17 of them completed the trial as per protocol and were included in the pharmacokinetic and safety analysis.
One subject (no. 14) withdrew on day 24 because of personal reasons.
All volunteers had a final visit and a telephonic follow-up.
The average demographic characteristics of the enrolled subjects are presented in the table:

Demographic data

Table 1. Demographic data

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<th>PARAMETER</th>
<th>N</th>
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<tr>
<td>Age (y)</td>
<td>18</td>
<td>27.6 ± 6.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>18</td>
<td>61.0 ± 10.6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>18</td>
<td>165.1 ± 6.2</td>
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The 18 enrolled volunteers were aged 20 to 39 years. One subject was Asian, the others were Caucasians. Weight did not differ significantly between the first and final visit for all the volunteers.

Study Medication
In the two cross-over study periods, volunteers were assigned to treatment A or B according to the randomisation where:
Treatment A: Merional B 300 IU for sc administration (test)
Treatment B: Merional B 300 IU for im administration (reference).

Measurements of the weights of the vials and of the syringe immediately before and after Merional injection showed that the actual amount injected was a little less than that anticipated. Therefore, individual PK parameters were corrected for the dose as following:
correction factor = 300/administered dose
Mean dose correction factor was 1.09 for treatment A and 1.13 for treatment B.

Pharmacokinetic results

The PK results are summarised in Tables 2 and 3 and Fig 1
Table 2. Mean FSH PK parameters after sc and im injection of Merional 300 IU (treatment A and B), corrected for the actual injected dose. n=17

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<th>C&lt;sub&gt;max&lt;/sub&gt; (IU/L)</th>
<th>t&lt;sub&gt;max&lt;/sub&gt; (h)</th>
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<td>292.2</td>
<td>23.5</td>
<td>46.7</td>
</tr>
<tr>
<td>MAX</td>
<td>12.0</td>
<td>30.0</td>
<td>680.5</td>
<td>722.6</td>
<td>64.9</td>
<td>97.6</td>
</tr>
</tbody>
</table>

(*) Mean Residence Time

Table 3. ANOVA comparison between FSH AUC<sub>t</sub> and C<sub>max</sub> after single sc and im administration of Merional 300 IU

<table>
<thead>
<tr>
<th>AUC&lt;sub&gt;t&lt;/sub&gt; (0-192 h)</th>
<th>ANOVA (N=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>p = 0.0132</td>
</tr>
<tr>
<td>Subject</td>
<td>p = 0.0009</td>
</tr>
<tr>
<td>Sequence</td>
<td>p = 0.0185</td>
</tr>
<tr>
<td>Point Estimate</td>
<td>1.13</td>
</tr>
<tr>
<td>90% Confidence interval</td>
<td>1.05 – 1.22</td>
</tr>
<tr>
<td>two one sided t test*</td>
<td>t&lt;sub&gt;L&lt;/sub&gt; = 2.3117</td>
</tr>
<tr>
<td></td>
<td>t&lt;sub&gt;U&lt;/sub&gt; = 7.9316</td>
</tr>
<tr>
<td>*t = 1.7531</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C&lt;sub&gt;max&lt;/sub&gt;</th>
<th>ANOVA (N=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>p = 0.0392</td>
</tr>
<tr>
<td>Subject</td>
<td>p = 0.0007</td>
</tr>
<tr>
<td>Sequence</td>
<td>p = 0.1340</td>
</tr>
<tr>
<td>Point Estimate</td>
<td>1.14</td>
</tr>
<tr>
<td>90% Confidence interval</td>
<td>1.03 – 1.27</td>
</tr>
<tr>
<td>two one sided t test *</td>
<td>t&lt;sub&gt;L&lt;/sub&gt; = 1.4657</td>
</tr>
<tr>
<td></td>
<td>t&lt;sub&gt;U&lt;/sub&gt; = 5.9840</td>
</tr>
<tr>
<td>*t = 1.7531</td>
<td></td>
</tr>
</tbody>
</table>

**FRIEDMAN NON PARAMETRIC TEST**

<table>
<thead>
<tr>
<th>t&lt;sub&gt;max&lt;/sub&gt;</th>
<th>p value</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.3320</td>
<td>NS</td>
</tr>
</tbody>
</table>

S = significant; NS = non significant; E = equivalent; NE = non equivalent.
The individual and mean ratios between treatment A and B for AUC_t and C_{max} of FSH were calculated and the mean ratio was 1.15\pm 0.26 for AUC_t and 1.18\pm 0.34 for C_{max}. AUC_t, C_{max}, and t_{max} of FSH obtained after sc administration were statistically compared with the same parameters obtained after im administration of 300 IU Merional (after correction for the actual dose). For AUC_t of FSH, although the difference between sc and im injection was statistically significant (p=0.013), the 90% CI was still within the acceptance range (90% CI 1.05−1.22). For C_{max} of FSH, there was a statistically significant between-group difference. Moreover, there was a large intra- and interindividual variability with the 90% CI outside the bioequivalence confidence intervals (90% CI=1.03−1.27).

With respect to FSH, a sequence effect was found for AUC_t but not for C_{max}. The differences between t_{max}, t_{1/2}, and MRT were found not statistically significant. Bioequivalence could be proven for MRT with the 90% CI=0.84−1.05. AUC_t, C_{max} and t_{max} of LH obtained after sc and im injection, respectively, were statistically compared. In contrast to FSH, mean AUC_t and C_{max} values of LH seemed to be larger after
im than after sc injection. However, the differences between the two administration routes were not statistically significant (p=0.625 and 0.249, respectively). For both AUCt and Cmax, bioequivalence could not be concluded (90% CI was 0.60–1.33 for AUCt and 0.58–1.11 for Cmax). Similar to the findings obtained for FSH, with LH a sequence effect was found for AUCt, but not for Cmax. The difference between mean tmax was found not statistically significant.

Assessor’s comments

With respect to the primary endpoint it would appear that the sc and the im route of administration show statistical differences with respect to both AUC and Cmax although the 90% CI was still within the acceptance range and appeared to be bioequivalent (90% CI=1.05–1.22) for AUC. However, with respect to Cmax of FSH, the 90% CI was outside the bioequivalence confidence intervals (90% CI=1.03–1.27), albeit, by 2%. It is notable that in the previous application bioequivalence study, the upper limit for Cmax 90% CI was identical at 1.27.

With respect to the PK parameters for LH which constituted the secondary endpoint, bioequivalence could not be concluded (90% CI was 0.60–1.33 for AUCt and 0.58–1.11 for Cmax). These findings appear to be notably similar, once again, to the results in the bioequivalence study of the previous application.

It is appreciated that there are design issues for bioequivalence studies due to the presence of endogenous hormones and necessity for baseline adjustment for the same as well as the inability to fully downregulate FSH and LH production. It would also be considered appropriate to determine bioequivalence on both components in the product; nevertheless differences in the biochemical profile of FSH and LH affect bioactivity and degradation. In the case of LH the short half life compared to FSH, poses particular problems.

II.1 Efficacy study
Study title:
A prospective, randomized, controlled clinical study on the assessment of tolerability and of clinical efficacy of Merional (hMG-IBSA) administered subcutaneously (sc) versus Merional administered intramuscularly (im) in women undergoing controlled ovarian hyperstimulation (COH) in an ART programme (IVF).

This was a phase III clinical study in compliance with GCP performed between December 14, 2001 and April 1, 2005 at 4 centres in Italy.

Objectives:
1. The evaluation of the clinical efficacy (in terms of oocytes recovered) of sc vs im Merional
2. The evaluation of local and systemic tolerability of sc vs im Merional

Number of patients:
A total of 163 women undergoing COH in an ART programme (IVF) were administered Merional im (80) or Merional sc (83).

Overall study design and plan description:
An overview of study procedures and assessments is given in table 4 below:
Table 4. Study procedures and assessments

<table>
<thead>
<tr>
<th>Phase</th>
<th>Visit</th>
<th>Investigations</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td></td>
<td>Blood chemistry and haematology&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pre-study assessment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FSH, LH, E&lt;sub&gt;2&lt;/sub&gt;, Scan</td>
<td></td>
</tr>
<tr>
<td>GnRHa down regulation</td>
<td>V1 (day 21 of previous cycle)</td>
<td></td>
<td>Start GnRHa, continue for ≥14 d, up to hCG trigger</td>
</tr>
<tr>
<td>hMG sc or im treatment</td>
<td>V2 (3&lt;sup&gt;rd&lt;/sup&gt; day of menses or after ≤10 days GnRHa), V2a (5 days after V2), V2b (5 days after V2a)</td>
<td>FSH, LH, E&lt;sub&gt;2&lt;/sub&gt;, Scan, AE, patient subjective intolerance and well being</td>
<td>Down regulation confirmed → start treatment</td>
</tr>
<tr>
<td></td>
<td>V3 (7 day after hMG start) to V7 (2-day intervals thereafter)</td>
<td>FSH, LH, E&lt;sub&gt;2&lt;/sub&gt;, Scan, AE, patient subjective intolerance and well being</td>
<td>Cycle monitoring up to ovarian response (follicle diameter)</td>
</tr>
<tr>
<td>hCG trigger</td>
<td>V3 to V8 (whenever ovarian response confirmed)</td>
<td>FSH, LH, E&lt;sub&gt;2&lt;/sub&gt;, Scan</td>
<td>Scan to assess number of mature follicles</td>
</tr>
<tr>
<td>Oocyte collection</td>
<td>V4 to V9 (whenever following hCG trigger)</td>
<td></td>
<td>Assessment of number of oocytes retrieved</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; Follow-up Visit (14 days after embryo transfer)</td>
<td>Blood chemistry and haematology&lt;sup&gt;a&lt;/sup&gt;, AE Urine pregnancy test</td>
<td>In case of positive pregnancy test plan Final Follow-up Visit</td>
</tr>
<tr>
<td></td>
<td>Final Follow-up Visit (28 days after embryo transfer)</td>
<td>Scan</td>
<td>Scan to determine number of implantations and embryonic heart beat</td>
</tr>
</tbody>
</table>

<sup>a</sup>erythrocytes, leukocytes, platelets, haemoglobin, haemocrit, AST, ALT, glycaemia, total bilirubin, BUN, γ-GT, creatinine

Inclusion criteria:
- infertile women with normal ovulatory cycles and with cause of infertility potentially solvable with IVF (eg PCO, tubal factor, endometriosis or unexplained fertility)
- undergoing ovarian stimulation for the purposes of oocyte retrieval in an assisted conception programme (using spouse’s semen)
- aged between 20 and 40 years
- body mass index (BMI) in the range 20–28 kg/m<sup>2</sup>
- early follicular phase FSH level <9 IU/l

Exclusion criteria:
- ascertained or presumptive hypersensitivity to the active principle and/or product ingredients
- primary ovarian failure
- ovarian cysts or enlargement not due to polycystic ovarian syndrome
- oocyte donation
- abnormal bleeding of undetermined origin
- patients showing poor response or requiring doses of more than 300IU daily in previous treatment cycles or those who have received similar therapies (previous treatment cycles) in the 30 days prior to the beginning of the study
- uncontrolled thyroid or adrenal dysfunction
- neoplasia
• severe impairment of the renal and/or hepatic functions
• diabetes and active thrombophlebitis, cardiopathies and epilepsy
• presence of clinically significant systemic disease or any contraindication of being pregnant and/or carrying out a pregnancy to term
• presence of any anatomical abnormality of the reproductive system
• being pregnant or breastfeeding
• menopause

Treatments administered:
Following admission into the study, patients were randomised to treatment with either Merional im or Merional sc according to their individual randomisation code and started a standard, long down-regulation protocol using 0.1 mg sc GnRH-agonist, once daily from day 21 of previous cycle up to pituitary down-regulation, confirmed by an ultrasound scan showing no evidence of ovarian activity, endometrial thickness <7 mm, and/or serum oestradiol ≤50 pg/ml (185 pmol/l). In case of cysts at ultrasound or endometrial thickness ≥7 mm, and 17β-oestradiol (E2) levels not basal, the patient was continued on GnRH-agonist for a further 5 days prior to start ovarian stimulation with study medication.

Following pituitary down regulation patients received Merional either im or sc, once daily (9.00–10.00am), until one follicle showed a mean diameter ≥18 mm and at least two follicles showed a mean diameter ≥16 mm, and in any case not for more than 18 days.

Finally, in presence of the leading follicle diameter ≥18 mm and at least two follicles diameter ≥16 mm, 5,000–10,000 IU of human chorionic gonadotrophin (hCG) (Profasi) was administered sc on the day following the last dose of Merional, 35–36 hours prior to the scheduled time of oocyte retrieval.

Test product:
Merional 75 IU/vial is a purified preparation of menotrophin, containing 75 IU of follicle stimulating hormone (FSH) activity and 75 IU of luteinising hormone (LH) activity, and is produced by IBSA Institut Biochimique sa, Switzerland using a own, patented purification method (patent application submitted Europe, USA, Canada, Australia, China, Israel).

Dose regimen:
The dose regimen chosen for ovulation induction was selected on the basis of patient's age and basal plasma FSH. In patients who had not previously undergone stimulation, those under 35 years were to receive 150 IU daily, and those 35–40 years were to receive 225 IU–300 IU daily, according to the hormonal ovarian status. The starting dose for patients who had undergone previous cycles was to be determined according to previous response.

The dosage was to be adjusted by the investigator starting from Day 7, according to the ovarian response, monitored by means of clinical examination, serum oestradiol levels and by ultrasonographic measurement of mean follicular diameter.

Primary endpoint:
• number of oocytes recovered (on the basis of which the actual study sample size was calculated)

Secondary endpoints:
• day of oocyte collection
• oestradiol AUC0-t and Cmax
• total dose of gonadotrophin (or no. of vials and no. of vials/day),
• number of mature follicles (follicles ≥16mm in diameter) on hCG day (or one day earlier),
• number of fertilized eggs*
• clinical pregnancy rate
* not foreseen by the protocol but analysed since considered important criterion.

Safety assessments:
• adverse events (AEs) (onset, severity, duration, drug relationship, seriousness, action/treatment required)
• OHSS risk (ovarian enlargement >10 cm, or follicular development in excess of >20 follicles, 17β-oestradiol levels >10,000pmol/l)
• local tolerability at the injection site
• haematological and biochemical laboratory test
• patient overall wellbeing

Statistical analyses:
Descriptive statistics were produced for demographic and physiologic data. Comparability of the treatment groups at baseline was assessed by Student t-test and χ², as appropriate.

The primary outcome variable, number of collected oocytes, was used to test equivalence according to Schuirmann test (two one-sided interval hypothesis test procedure), and to define its 90%CI, with treatments considered equivalent in case of differences not exceeding ±20%. The same statistical approach was applied to secondary outcome variables: day of oocyte collections, number of mature follicles (≥16mm) on hCG Day, AUC₀₋ₜ of 17β-oestradiol (calculated according to trapezoidal rule and adjusted with respect to baseline), Cₘₐₓ of 17β-oestradiol, total dose of gonadotrophin. Between treatment differences for all continuous efficacy variables showing normal data distribution was tested by unpaired Student-t-test, while in presence of non-normal value distribution, the non parametric Mann-Whitney U test was used. Between treatment differences of binomial efficacy variables (pregnancy rate, foetal heart beat rate) were tested by χ² test.

According to study protocol, the analysis of the primary end-point was carried out in all treated patients, with missing values for patients not submitted to oocytes collection replaced by zero. In addition, a confirmatory analysis of the primary end-point was carried out in all patients completing the study with oocyte collection, ie after exclusion of the seven and six patients treated with im and sc hMG, respectively, who did not undergo oocytes collection.

Patient disposition:
Patient disposition is summarised in Figure 2 below.
A total of 80 and 83 patients started hMG treatment, with 73 (91.2%) and 77 patients (92.8%) (im and sc respectively) completing it up to oocyte collection.

One patient died due to a car accident. Two patients per group discontinued hMG treatment because of OHSS risk. Other reasons for not completing the study up to oocyte collection were occasionally reported in either group, with no treatment related pattern.
Table 5. Patient disposition and reasons for not completing the study up to oocyte collection

<table>
<thead>
<tr>
<th>Patient Disposition</th>
<th>Merional(^{sc})</th>
<th>Merional(^{im})</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Protocol completed</td>
<td>77</td>
<td>90.6</td>
<td>73</td>
</tr>
<tr>
<td>Down regulation failed</td>
<td>2</td>
<td>2.3</td>
<td>1</td>
</tr>
<tr>
<td>Down regulation not completed</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td>Risk of hyperstimulation</td>
<td>2</td>
<td>2.3</td>
<td>2</td>
</tr>
<tr>
<td>Monofollicular response</td>
<td>2</td>
<td>2.3</td>
<td>1</td>
</tr>
<tr>
<td>Oocyte recovery not performed</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Adverse event (death)</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Severe male factor</td>
<td>1</td>
<td>1.2</td>
<td>0</td>
</tr>
<tr>
<td>hMG administration for &gt;18 days</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Decapeptyl intake interrupted before oocyte recovery</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Cycle cancelled for coasting</td>
<td>1</td>
<td>1.2</td>
<td>0</td>
</tr>
</tbody>
</table>

Demographics

Demographic and baseline characteristics by treatment group are described below.

Table 6. Demographic and baseline characteristics by treatment group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>Merional(^{sc})</td>
<td>83</td>
<td>33.11</td>
<td>3.43</td>
<td>22</td>
<td>40</td>
<td>0.1166*</td>
</tr>
<tr>
<td></td>
<td>Merional(^{im})</td>
<td>80</td>
<td>32.23</td>
<td>3.71</td>
<td>23</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Height (m)</td>
<td>Merional(^{sc})</td>
<td>83</td>
<td>1.63</td>
<td>0.06</td>
<td>1.47</td>
<td>1.80</td>
<td>0.9438*</td>
</tr>
<tr>
<td></td>
<td>Merional(^{im})</td>
<td>80</td>
<td>1.62</td>
<td>0.06</td>
<td>1.50</td>
<td>1.80</td>
<td></td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>Merional(^{sc})</td>
<td>83</td>
<td>69.20</td>
<td>7.55</td>
<td>44.3</td>
<td>81.0</td>
<td>0.9895*</td>
</tr>
<tr>
<td></td>
<td>Merional(^{im})</td>
<td>80</td>
<td>69.21</td>
<td>6.93</td>
<td>50.0</td>
<td>80.0</td>
<td></td>
</tr>
<tr>
<td>Body Mass Index (g/m²)</td>
<td>Merional(^{sc})</td>
<td>83</td>
<td>22.76</td>
<td>2.45</td>
<td>20.0</td>
<td>27.9</td>
<td>0.8621*</td>
</tr>
<tr>
<td></td>
<td>Merional(^{im})</td>
<td>80</td>
<td>22.82</td>
<td>2.24</td>
<td>20.0</td>
<td>27.7</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>Merional(^{sc})</td>
<td>83</td>
<td>72.17</td>
<td>9.31</td>
<td>60</td>
<td>110</td>
<td>0.7917*</td>
</tr>
<tr>
<td></td>
<td>Merional(^{im})</td>
<td>80</td>
<td>72.63</td>
<td>12.43</td>
<td>60</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>Merional(^{sc})</td>
<td>83</td>
<td>113.92</td>
<td>12.12</td>
<td>60</td>
<td>140</td>
<td>0.4526*</td>
</tr>
<tr>
<td></td>
<td>Merional(^{im})</td>
<td>80</td>
<td>112.50</td>
<td>11.88</td>
<td>70</td>
<td>140</td>
<td></td>
</tr>
<tr>
<td>Heart Rate (beats/min)</td>
<td>Merional(^{sc})</td>
<td>83</td>
<td>72.17</td>
<td>5.75</td>
<td>60</td>
<td>86</td>
<td>0.3830*</td>
</tr>
<tr>
<td></td>
<td>Merional(^{im})</td>
<td>80</td>
<td>71.40</td>
<td>5.47</td>
<td>55</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>Previous IVF cycles</td>
<td>Merional(^{sc})</td>
<td>83</td>
<td>0.48</td>
<td>1.03</td>
<td>0</td>
<td>6</td>
<td>0.0396*</td>
</tr>
<tr>
<td></td>
<td>Merional(^{im})</td>
<td>80</td>
<td>0.76</td>
<td>1.21</td>
<td>0</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Infertility duration (years)</td>
<td>Merional(^{sc})</td>
<td>83</td>
<td>4.98</td>
<td>2.60</td>
<td>2</td>
<td>14</td>
<td>0.9159*</td>
</tr>
<tr>
<td></td>
<td>Merional(^{im})</td>
<td>80</td>
<td>5.06</td>
<td>2.89</td>
<td>1</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

*Between treatment difference, Student’s t test† Between treatment difference, Mann-Whitney U test

The Merional \(^{sc}\) and \(^{im}\) treatment groups were similar in terms of age (mean±SD 33.1±3.4 vs 32.2 ±3.7 years, respectively), as well as physical parameters and vital signs, with no statistically significant between treatment differences at Student’s t test. Infertility duration was similar in the two groups (mean±SD 4.98±2.60 vs 5.06±2.89 years, respectively), while the mean number of previous
unsuccessful IVF cycles was lower in the sc treatment group (0.48 on the average than in the im treatment group (0.76 on average), with statistically significant between treatment differences at Mann-Whitney U test (p<0.05).

Absolute and percent frequency of patients with previous spontaneous or induced pregnancy is shown below.

Table 7. Absolute and percent frequency of patients with previous pregnancy/ies by treatment group

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Merional&lt;sup&gt;®&lt;/sup&gt; sc (n=83)</th>
<th>Merional&lt;sup&gt;®&lt;/sup&gt; im (n=80)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with previous pregnancy/ies</td>
<td>25</td>
<td>22</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Patients with previous spontaneous pregnancy/ies</td>
<td>22</td>
<td>19</td>
<td>26.5</td>
</tr>
<tr>
<td>Patients with previous induced pregnancy/ies</td>
<td>3</td>
<td>4</td>
<td>3.6</td>
</tr>
</tbody>
</table>

* on patients with previous pregnancy/ies

NB: patient nb 433 had a previous ectopic pregnancy and was not included in the statistical analysis.

The Merional sc and im treatment groups were similar in terms of percent frequency of patients with previous pregnancy/ies (30.1% vs 27.5%, respectively), either spontaneous (26.5% vs 23.7%, respectively), or induced (3.6% vs 5.0%, respectively).

Changes to the conduct of the study
The second protocol amendment changed the study endpoint from a pharmacodynamic measure, i.e. 17β-oestradiol AUC to one of clinical efficacy (number of oocytes retrieved) and a consequential increase in sample size. These changes were to reflect current thinking in terms of evaluating treatment effectiveness.

Efficacy results
Primary endpoint: mean number of collected oocytes was lower in the sc than in the im group (mean value±SD 7.46±4.24 vs 7.86±4.28, respectively). Analysis of all treated patients showed therapeutic bioequivalence of the two administration routes.

A confirmatory analysis of the primary end-point was carried out in all patients completing the study with oocyte collection, ie after exclusion of the seven and six patients treated with im and sc Merional, respectively, who did not undergo oocyte collection. Mean number of collected oocytes was similar between the sc and im Merional groups (8.04±3.83 vs 8.62±3.68). Statistical analysis confirmed therapeutic bioequivalence between the two groups as for the primary study endpoint.

Table 8. Bioequivalence statistic for the primary end-point (number of oocytes retrieved)

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>TREATMENT</th>
<th>N&lt;sup&gt;°&lt;/sup&gt;</th>
<th>MEAN±SD</th>
<th>SC-IM DIFFERENCE</th>
<th>LOWER LIMIT</th>
<th>UPPER LIMIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of oocytes collected (ITT population)</td>
<td>Merional&lt;sup&gt;®&lt;/sup&gt; s.c.</td>
<td>83</td>
<td>7.46±4.24</td>
<td>-0.40</td>
<td>0.04</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Merional&lt;sup&gt;®&lt;/sup&gt; i.m.</td>
<td>80</td>
<td>7.86±4.28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of oocytes collected (PP population)</td>
<td>Merional&lt;sup&gt;®&lt;/sup&gt; s.c.</td>
<td>77</td>
<td>8.04±3.83</td>
<td>-0.58</td>
<td>0.03</td>
<td>p=0.0001</td>
</tr>
<tr>
<td></td>
<td>Merional&lt;sup&gt;®&lt;/sup&gt; i.m.</td>
<td>73</td>
<td>8.62±3.68</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Secondary endpoints: no statistically significant differences were seen, except for day of oocyte collection, which was significantly shorter (p<0.05) in the sc compared with the im group (mean value±SD: 13.82±1.73 vs 14.58±2.11 days, respectively). Merional intake was significantly less (p<0.01) in the sc group in relation to the im group (mean value±SD: 2168±729.55 vs 2595.09±951.21IU, respectively).

Table 9. Descriptive statistic of secondary end-points

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>TREATMENT</th>
<th>N⁰</th>
<th>MEAN ± SD</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of oocytes collected</td>
<td>Merional® sc.</td>
<td>83</td>
<td>7.46 ± 4.24</td>
<td>0.26⁰</td>
</tr>
<tr>
<td></td>
<td>Merional® i.m.</td>
<td>80</td>
<td>7.36 ± 4.28</td>
<td></td>
</tr>
<tr>
<td>Day of oocyte collection</td>
<td>Merional® sc.</td>
<td>77</td>
<td>13.82 ± 1.73</td>
<td>0.02⁰</td>
</tr>
<tr>
<td></td>
<td>Merional® i.m.</td>
<td>73</td>
<td>14.28 ± 2.11</td>
<td></td>
</tr>
<tr>
<td>Total dose of gonadotrophin (IU)</td>
<td>Merional® sc.</td>
<td>82</td>
<td>2168.60 ± 729.55</td>
<td>&lt;0.01⁰</td>
</tr>
<tr>
<td></td>
<td>Merional® i.m.</td>
<td>79</td>
<td>2595.09 ± 951.21</td>
<td></td>
</tr>
<tr>
<td>No mature follicles (≥ 16 mm) on hCG</td>
<td>Merional® sc.</td>
<td>78</td>
<td>8.82 ± 4.14</td>
<td>0.07⁰</td>
</tr>
<tr>
<td></td>
<td>Merional® i.m.</td>
<td>74</td>
<td>8.80 ± 3.36</td>
<td></td>
</tr>
<tr>
<td>No of fertilized eggs</td>
<td>Merional® sc.</td>
<td>83</td>
<td>3.36 ± 2.68</td>
<td>0.44⁰</td>
</tr>
<tr>
<td></td>
<td>Merional® i.m.</td>
<td>82</td>
<td>3.98 ± 3.00</td>
<td></td>
</tr>
<tr>
<td>17β-estradiol Cmax (pmol/l))</td>
<td>Merional® sc.</td>
<td>82</td>
<td>7.54 ± 0.80</td>
<td>0.25⁰</td>
</tr>
<tr>
<td></td>
<td>Merional® i.m.</td>
<td>78</td>
<td>7.66 ± 0.51</td>
<td></td>
</tr>
</tbody>
</table>

⁰ Between treatment difference, Student’s t test
⁰ Between treatment difference, Mann-Whitney U test.

Secondary binomial efficacy variables:
Absolute and percent frequency of pregnancy and of foetal heart beat in the 77 and 72 patients of the sc and im treatment group, respectively, who had urine pregnancy test performed 14 days after embryo transfer is shown below.

Table 10. Absolute and percent frequency of pregnancy and foetal heart beat by treatment group

<table>
<thead>
<tr>
<th>Presence of</th>
<th>Merional® sc</th>
<th>Merional® im</th>
<th>χ² test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=77)</td>
<td>(n=72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>32</td>
<td>25</td>
<td>34.7</td>
<td>0.3938</td>
</tr>
<tr>
<td></td>
<td>41.6%</td>
<td>34.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foetal heart beat</td>
<td>21</td>
<td>19</td>
<td>23.7</td>
<td>0.8180</td>
</tr>
<tr>
<td></td>
<td>25.3%</td>
<td>23.7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pregnancy rate was greater in the sc treatment group than in the im treatment group (41.6% vs 34.7%, respectively), while heart beat rates were similar (25.3% vs 23.7%, respectively). There was no significant difference between treatments for either variable.

Assessor's comment on efficacy
The applicant has additionally provided the output from an analysis of variance (ANOVA) including 90% and 95% confidence intervals for the primary endpoint, i.e. difference in the mean number of oocytes in each treatment arm. Results of the analysis of variance (ANOVA) with a 90% CI, shows that the two treatment groups are equivalent in term of mean number of oocytes retrieved. When the same analysis is performed with a 95% CI, the upper confidence limit is outside of the pre-specified limits (i.e. 20% of the mean number of oocytes retrieved in the reference –i.m. group). The 20% equivalence limit used in the study resulted in a definition of equivalence that is considerably more stringent than a definition based on clinical relevance. If an equivalence limit of a clinically relevant
difference of 2 oocytes is used, then the equivalence of the formulations has been demonstrated regardless of whether 90% or 95% confidence intervals are used.

The results for the secondary endpoints with respect to day of oocyte collection and number of mature follicles appeared to be similar, however, the former was statistically significantly lower in the sc group compared to the im group, 13.81 versus 14.47 days. Both these endpoints were deemed to be equivalent by the applicant.

Demonstration of clinical benefit is considered to supersede lack of pharmacokinetic bioequivalence. It can therefore be considered that results from the efficacy study support bioequivalence between the sc and im route of administration for Merional. This is acceptable.

III. STATISTICAL ASSESSMENT OF EFFICACY

This is a national variation to a licence for Merional to add a subcutaneous route of administration to the already granted intramuscular formulation. The application consists of a single therapeutic equivalence study, HMG06 and a pharmacokinetic study, PK003.

III.1 Study HMG06

Study design
This was a prospective randomised controlled trial to assess the tolerability clinical efficacy of Merional administered subcutaneously versus Merional administered intramuscularly in women undergoing controlled ovarian hyperstimulation (COH) in an ART programme (IVF). At the beginning of the trial, 168 patients were randomised and prior to treatment, patients started GnRH-agonist down regulation. Of these 168 patients, 163 successfully downregulated and were randomised to receive either Merional sc or Merional im (83 and 80 respectively). The dose used depended on a routine range, depending on the ovarian response (a smaller dose being used in response to a greater ovarian response).

The original primary endpoint was a pharmacodynamic measure, $17\beta$-oestradiol AUC. A protocol amendment changed this to one of clinical efficacy (number of oocytes retrieved) and resulted in a consequential increase in sample size. These changes were to reflect current thinking in terms of evaluating treatment effectiveness.

**Statistical assessor’s comment:**
The decision to switch from a pharmacodynamic to an efficacy study is acceptable, although the pharmacodynamic endpoints are still important and are appropriately defined as key secondary endpoints.

Analysis methods
The pre-specified analysis plan stated that the treatments were to be considered equivalent if the difference did not exceed ± 20%. The company proposed two one-sided hypothesis tests at the 5% level.

**Statistical assessor’s comment:**
The study design is acceptable in general. The applicant has provided ANOVA results with a 90% CI (which show that the two treatment groups are equivalent in term of mean number of oocytes retrieved) and a 95% CI. With a 95% CI, the upper confidence limit is outside of the pre-specified limits (i.e. 20% of the mean number of oocytes retrieved in the reference –i.m. group). Using this definition s.c. administration is not equivalent to the i.m. administration as the study was designed to demonstrate equivalence based on 90% confidence intervals and the equivalence limits specified in
the protocol. Hence, it is underpowered with respect to equivalence based on 95% confidence intervals.

The 20% equivalence limit used in the study resulted in a definition of equivalence that is considerably more stringent than a definition based on clinical relevance. If an equivalence limit of a clinically relevant difference of 2 oocytes is used, then the equivalence of the formulations has been demonstrated regardless of whether 90% or 95% confidence intervals are used.

It is of note that the failure to demonstrate equivalence is only in the ITT and not the per-protocol population. Usually for equivalence trials the PP population is the most sensitive. In this trial, because the ITT population includes a large number of patients with 0 oocytes retrieved, this lowers the point estimate, which additionally tightens the acceptance criteria. It is noted that in all analyses, the company is well within +/- 2 oocytes, and so failure to formally demonstrate efficacy in the ITT population may not be a major concern, however the clinical argumentation is acceptable.

Patient disposition
The patient disposition table is shown below.

Table 3. Patient disposition

Statistical assessor's comment:
There is a similar amount of missing data in the 2 groups and the applicant has addressed the patient disposition satisfactorily.

Results
The applicant has provided the following data as proof of equivalence.
Table 11. Mean number (mean±SD) of collected oocytes (ITT and PP populations) following Merional treatment (sc and im)

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>TREATMENT</th>
<th>N°</th>
<th>MEAN ± SD</th>
<th>SC-IM DIFFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>N° of oocytes collected (ITT population)</td>
<td>Merional® s.c.</td>
<td>83</td>
<td>7.46 ± 4.24</td>
<td>-0.40</td>
</tr>
<tr>
<td></td>
<td>Merional® i.m.</td>
<td>80</td>
<td>7.86 ± 4.28</td>
<td></td>
</tr>
<tr>
<td>N° of oocytes collected (PP population)</td>
<td>Merional® s.c.</td>
<td>77</td>
<td>8.04 ± 3.83</td>
<td>-0.58</td>
</tr>
<tr>
<td></td>
<td>Merional® i.m.</td>
<td>73</td>
<td>8.62 ± 3.68</td>
<td></td>
</tr>
</tbody>
</table>

Table 12. Number of collected oocytes in all treated patients: 5% confidence limits (CL) [lower limit (LL), upper limit (UL)] of mean between treatment difference, t-value and p-value

<table>
<thead>
<tr>
<th>5% CL</th>
<th>Mean difference</th>
<th>t-value</th>
<th>One-sided p-value to reject non-equivalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>specified</td>
<td>observed</td>
<td>specified</td>
</tr>
<tr>
<td>LL</td>
<td>-1.5725</td>
<td>-1.5093</td>
<td>1.6544</td>
</tr>
<tr>
<td>UL</td>
<td>1.5725</td>
<td>0.7000</td>
<td>-1.6544</td>
</tr>
</tbody>
</table>

Statistical assessor’s comment:
The applicant has provided 90% confidence intervals for the absolute and relative mean differences and 95% confidence limits that are more appropriate for equivalence studies.

The 90% confidence intervals for AUC and C_{max} are outside the standard 80–125% acceptance criteria. The applicant argues that the trial was not specifically powered to demonstrate formal bioequivalence, and this is acknowledged. However, the clinical results can be considered to supersede this.

The applicant has also provided the secondary analysis for the pharmacodynamic endpoint 17β-oestradiol (the original primary endpoint).

Table 13. AUC

<table>
<thead>
<tr>
<th>Statistics</th>
<th>Merional® sc</th>
<th>Merional® im</th>
<th>sc–im difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>8.7044</td>
<td>8.8097</td>
<td>-0.1053</td>
</tr>
<tr>
<td>SD</td>
<td>0.6350</td>
<td>0.5205</td>
<td></td>
</tr>
<tr>
<td>SE</td>
<td>0.0701</td>
<td>0.0589</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>8.7594</td>
<td>8.8401</td>
<td></td>
</tr>
<tr>
<td>Min</td>
<td>6.9991</td>
<td>7.5632</td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>10.2082</td>
<td>9.9659</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>82</td>
<td>78</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5% CL</th>
<th>Mean difference</th>
<th>t-value</th>
<th>One-sided p-value to reject non-equivalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>specified</td>
<td>observed</td>
<td>specified</td>
</tr>
<tr>
<td>LL</td>
<td>-0.2231</td>
<td>-0.2576</td>
<td>1.6546</td>
</tr>
<tr>
<td>UL</td>
<td>0.2231</td>
<td>0.0470</td>
<td>-1.6546</td>
</tr>
</tbody>
</table>
Table 14. $C_{\text{max}}$

<table>
<thead>
<tr>
<th>Statistics</th>
<th>Merional* sc</th>
<th>Merional* im</th>
<th>sc–im difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>7.5435</td>
<td>7.6637</td>
<td>-0.1202</td>
</tr>
<tr>
<td>SD</td>
<td>0.5976</td>
<td>0.5129</td>
<td></td>
</tr>
<tr>
<td>SE</td>
<td>0.0660</td>
<td>0.0581</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>7.5787</td>
<td>7.6833</td>
<td></td>
</tr>
<tr>
<td>Min</td>
<td>5.8999</td>
<td>6.3333</td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>8.8155</td>
<td>8.9049</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>82</td>
<td>78</td>
<td></td>
</tr>
</tbody>
</table>

5% CL

<table>
<thead>
<tr>
<th></th>
<th>Mean difference</th>
<th>t-value</th>
<th>One-sided p-value to reject non-equivalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>specified</td>
<td>observed</td>
<td>specified</td>
</tr>
<tr>
<td>LL</td>
<td>-0.2231</td>
<td>-0.2662</td>
<td>1.6546</td>
</tr>
<tr>
<td>UL</td>
<td>0.2231</td>
<td>0.0258</td>
<td>-1.6546</td>
</tr>
</tbody>
</table>

The applicant states that therapeutic equivalence between treatment groups was not demonstrated for the secondary endpoint. As already discussed, the failure to demonstrate bioequivalence is superseded by the efficacy data. This is acceptable.

III.2 Pharmacokinetic study PK003

This was a 2-period cross-over study designed to compare the pharmacokinetics of Merional administered iv and sc. The study enrolled 17 patients and blood samples were taken at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 16 hours on the first day, followed by samples at 24, 30, 36, 48, 72, 96, 144 and 192 hours. Wash out between the treatments was 14 days.

Results

Table 15. ANOVA results

<table>
<thead>
<tr>
<th>ANOVA (N=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>Subject</td>
</tr>
<tr>
<td>Sequence</td>
</tr>
<tr>
<td>Point Estimate</td>
</tr>
<tr>
<td>90% Confidence interval</td>
</tr>
<tr>
<td>two one sided t test*</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*$_t = 1.7531$

<table>
<thead>
<tr>
<th>C_{max}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>Subject</td>
</tr>
<tr>
<td>Sequence</td>
</tr>
<tr>
<td>Point Estimate</td>
</tr>
<tr>
<td>90% Confidence interval</td>
</tr>
<tr>
<td>two one sided t test*</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*$_t = 1.7531$
**Statistical assessor’s comment:**
The 90% confidence intervals for AUC and $C_{\text{max}}$ are outside the standard 80–125% acceptance criteria. The applicant argues that the trial was not specifically powered to demonstrate formal bioequivalence, and this is acknowledged. However, the clinical results can be considered to supersede this.

The applicant has provided sufficient evidence for the potential lack of carryover, based on the predose measurements all being lower or equal at the start of the second period.

**Statistical assessor’s conclusion:**
The failure to demonstrate bioequivalence is superseded by the efficacy data. This is acceptable.

### IV. SAFETY
Safety data was evaluated from the PK and efficacy clinical studies submitted in support of this application:
1. Comparative PK study comparing sc to im administration of hMG in female healthy volunteers (Study CRO-PK-00-30)
2. A prospective, randomised, controlled clinical study on the assessment of tolerability and clinical efficacy of Merional administered sc versus Merional administered im in women undergoing COH in an ART programme (IVF) (00IF/HMG06)

Safety assessment was based on adverse events (AE) (onset, severity, duration, drug relationship, seriousness, action/treatment required), OHSS risk, local tolerability at injection site, haematological and biochemical laboratory test, patient overall well-being.

**Overall extent of exposure**
Overall extent of exposure of patients to Merional is displayed in table 16 below.

<table>
<thead>
<tr>
<th>Duration (Days)</th>
<th>0 &lt; Dose ≤ 75</th>
<th>75 &lt; Dose ≤ 150</th>
<th>150 &lt; Dose ≤ 225</th>
<th>225 &lt; Dose ≤ 300</th>
<th>300 &lt; Dose ≤ 375</th>
<th>375 &lt; Dose ≤ 450</th>
<th>Total (any dose)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 &lt; Dur ≤ 5</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td>11.05</td>
</tr>
<tr>
<td>5 &lt; Dur ≤ 10</td>
<td></td>
<td>10</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td>41</td>
<td>22.65</td>
</tr>
<tr>
<td>10 &lt; Dur ≤ 20</td>
<td></td>
<td>40</td>
<td>50</td>
<td>1</td>
<td></td>
<td></td>
<td>112</td>
<td>61.88</td>
</tr>
<tr>
<td>15 &lt; Dur ≤ 20</td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>1</td>
<td></td>
<td></td>
<td>8</td>
<td>4.42</td>
</tr>
<tr>
<td>20 ≤ Dur</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Total (any duration)</td>
<td>2</td>
<td>59</td>
<td>57</td>
<td>60</td>
<td>2</td>
<td>1</td>
<td>181</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**Demographics**
The demography of patients (n=163) and healthy volunteers (n=18) enrolled in the two studies that are evaluable for safety are shown in table 17 below.
Table 17. Demographic profile of patients enrolled

<table>
<thead>
<tr>
<th></th>
<th>ALL COMPLETED (N = 199)</th>
<th>MERIONAL I.M. (N = 98)</th>
<th>MERIONAL S.C. (N = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 18</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>18 – 65</td>
<td>199</td>
<td>0</td>
<td>83 + 18 =</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Females</td>
<td>199</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Black</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Caucasian</td>
<td>198</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other factors</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

ADVERSE EVENTS

Study CRO-PK-00-30: six AEs were experienced by five subjects. Four AEs were short episodes of headache of moderate intensity, in one case accompanied by nausea, deemed not related to study drug. One subject experienced a haematoma at injection site (sc). No serious AEs were reported during the study.

Apart from the haematoma already mentioned, no local reactions were reported and no apparent differences with respect to the local tolerability were observed between the two administration routes.

No relevant changes from baseline occurred at final visit for laboratory parameters. All values outside the normal ranges were considered not clinically relevant.

Study 00IF/HMG06: three patients experienced AEs considered possibly or definitely related to study medication, one patient in the sc group (OHSS) and two patients in the im group (abdominal pain and OHSS respectively).

Serious AEs occurred in two patients from the im group (OHSS and car accident respectively) and in one patient in the sc group (OHSS).

The incidence of AEs in each study is detailed below:
Table 18. Incidence of AEs in individual studies (ART)

<table>
<thead>
<tr>
<th>BODY SYSTEM / ADVERSE EFFECT</th>
<th>MERONAL STUDY 00CRO-PK-00-30 (Module 5.3.1.2)</th>
<th>MERONAL STUDY 00IF/HMG06 (Module 5.3.5.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALL DOSES (N = 199) IM. (N = 18) SC. (N = 18) IM. (N = 80) SC. (N = 83)</td>
<td></td>
</tr>
<tr>
<td><strong>REPRODUCTIVE SYSTEM AND BREAST DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian hyperstimulation</td>
<td>2 (1.01%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%)</td>
<td></td>
</tr>
<tr>
<td>Breast discomfort</td>
<td>0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%)</td>
<td></td>
</tr>
<tr>
<td>Breast pain</td>
<td>0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%)</td>
<td></td>
</tr>
<tr>
<td>Metrorrhagia</td>
<td>0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%)</td>
<td></td>
</tr>
<tr>
<td><strong>NERVOUS SYSTEM DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>5 (2.51%) 3 (16.67%) 1 (5.55%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%)</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%)</td>
<td></td>
</tr>
<tr>
<td><strong>PSYCHIATRIC DISORDERS</strong></td>
<td></td>
<td></td>
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<tr>
<td>Mood swings</td>
<td>0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%)</td>
<td></td>
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<tr>
<td><strong>GI SYSTEM DISORDERS</strong></td>
<td></td>
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<tr>
<td>Dry mouth</td>
<td>0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (0.50%) 1 (5.55%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%)</td>
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</tr>
<tr>
<td>Abdominal discomfort</td>
<td>0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (0.50%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%)</td>
<td></td>
</tr>
<tr>
<td>Abdominal distension</td>
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</tr>
<tr>
<td>Abdominal tenderness</td>
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</tr>
<tr>
<td><strong>INFECTIONS AND INFESTATIONS</strong></td>
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<td></td>
</tr>
<tr>
<td>Influenza</td>
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<td></td>
</tr>
<tr>
<td><strong>CARDIAC DISORDERS</strong></td>
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<td></td>
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<tr>
<td>Palpitations</td>
<td>0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0 (0.00%)</td>
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</tr>
<tr>
<td>BODY SYSTEM / ADVERSE EFFECT</td>
<td>MERIONAL STUDY 00CR0-PK-06-30 (MODULE 5.3.1.2)</td>
<td>MERIONAL STUDY 00IF/HMG06 (MODULE 5.3.5.1)</td>
</tr>
<tr>
<td>------------------------------</td>
<td>---------------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>ALL DOSES (N = 199)</td>
<td>I.M. (N = 18)</td>
</tr>
<tr>
<td>METABOLISM AND NUTRITION DISORDERS</td>
<td></td>
<td>S.C. (N = 18)</td>
</tr>
<tr>
<td>• Decreased appetite</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>• Feeling abnormal</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>• Fatigue</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>• Injection site pain</td>
<td>11 (5.53%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>• Injection site hematoma</td>
<td>1 (0.50%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>• Chills</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>• Back pain</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</td>
<td></td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</td>
<td></td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>• Hyperhydrosis</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>• Hot flushes</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>INVESTIGATIONS</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>• Weight increased</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>TOTAL NUMBER (%) OF AEs</td>
<td>21 (10.55%)</td>
<td>4 (22.22%)</td>
</tr>
<tr>
<td></td>
<td>2 (11.11%)</td>
<td>13 (16.25%)</td>
</tr>
<tr>
<td></td>
<td>2 (4.11%)</td>
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</table>

Patient withdrawals in each study is presented below.
Table 19. Patient withdrawal by study

<table>
<thead>
<tr>
<th>STUDIES</th>
<th>TOTAL WITHDRAWAL</th>
<th>REASON FOR WITHDRAWAL</th>
<th>N° WITHOUT POSTWITHDRAWAL EFFICACY DATA</th>
</tr>
</thead>
<tbody>
<tr>
<td>N°/ID</td>
<td>Drug</td>
<td>M/F</td>
<td>AGE &gt; 65</td>
</tr>
<tr>
<td>---------</td>
<td>------------------</td>
<td>----------------------</td>
<td>---------</td>
</tr>
<tr>
<td>CRO-PK-00-30</td>
<td>Merional i.m. (N = 18)</td>
<td>1 M/1 F</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Merional s.c. (N = 18)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>00IF/HMG06</td>
<td>Merional i.m. (N = 80)</td>
<td>7 M/7 F</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Merional s.c. (N = 83)</td>
<td>6 M/6 F</td>
<td>0</td>
</tr>
</tbody>
</table>

Deaths
One death occurred in study 00IF/HMG06 (car accident) however this was considered unrelated to treatment.

Serious adverse events (SAEs)
In study 00IF/HMG06 one patient in the im group suffered OHSS (mild and definite) and one patient in the sc group suffered OHSS (severe and definite).
No SAEs were reported in study CRO-PK-00-30.

Clinical laboratory evaluation
No significant effects of Merional on blood chemistry and haematology were noted in either clinical study.

Vital signs, physical findings and other observations related to study
No detrimental effect of Merional on vital sign or physical finding was observed in either study.

Other findings
No drug interactions were reported for either study.

IV.1 Post marketing safety data
Merional (75 IU/ml and 150 IU/ml) was first granted in Cyprus on July 1991 and is now authorised in 26 countries and marketed in 25 countries worldwide. The EEA countries in which Merional is
authorised are: United Kingdom, Bulgaria, Hungary, Slovak Republic, Czech Republic, Greece and Cyprus.

Taking into account the different dosages administered for anovulation therapy (mean daily dose 150IU for mean therapy duration of 12 days) and controlled ovarian stimulation during ART therapy (mean daily dose 300IU for mean therapy duration of 11 days), the MAH has estimated that a range from 294,612 to 540,122 cycles, depending on the indication, have been performed with Merional 75IU/ml and 150IU/ml worldwide since 1996.

From 1991 to April 2008, six serious adverse drug reactions (SADRs), three listed and two unlisted have been received from regulatory authorities and one serious listed ADR has been received from a health care professional. One non-serious unlisted spontaneous case has been assessed as unlisted due to the severity of the event.

A PubMed review revealed seven SADRs related to the use of HMGs. One was a fatal case and was assessed as unlisted; five were evaluated as listed.

Most of the reported events were of OHSS associated to thrombotic events.

One serious case reported the occurrence of gestational trophoblastic disease (GTD) and ruptured ectopic pregnancy. Trophoblast cells are derived from the embryo and are responsible for the formation of the placenta. Gestational trophoblastic disease (GTD) is a spectrum of disorders, ranging from hydatidiform mole to choriocarcinoma and placental site tumour. A variety of risk factors have been implicated in GTD, but aetiology remains uncertain. The available data do not confirm a potential association between infertility, its treatment and GTD.

No new, relevant safety findings with a potential impact on the overall safety of the product have been collected and identified. There have been no reports of drug interactions, and no experience with deliberate or accidental overdose, or drug abuse or misuse.

No experiences during pregnancy or lactation as well as in special patient groups were collected.

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**Assessor’s comments on safety**

With respect to the randomised controlled efficacy clinical trial, the incidence of treatment-emerging AEs appeared to be low in the two groups (2.4% vs 3.7% of the 83 and 80 patients exposed to sc and im treatment, respectively). The AEs possibly or definitely related to study medication occurred in 1 and 2 patients, respectively, and serious AEs in 2 patients for the im group and 1 patient in the sc group.

Mean values and changes of haematology and blood chemistry tests or in the frequency distribution of modifications to abnormal findings at follow up assessment vs baseline were unremarkable. Similarly, the frequency of well-being classifications between the groups was also unremarkable, with full well-being highly prevalent and mildly unwell condition generally accounting for remaining cases in both groups.

More importantly, no differences were apparent with respect to the frequency of OHSS or OHSS risk, however, the incidence of OHSS was very low (<2.0%).

Pain at injection site was complained of only in the im group, in 13.9% of patients, with a statistically highly significant difference (p<0.001).

With respect to the PK study in female healthy volunteers, the limited safety data did not raise any particular concerns however it should be noted that this was just a single dose crossover study. Overall, the safety data which are limited would appear to suggest that tolerability and safety were similar in both treatment groups.
IV.2 Pharmacovigilance system and risk management plan

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The applicant has provided a Risk Management Plan that is considered to adequately monitor identified and potential risks in relation to suspected adverse reactions.

V. OVERALL CONCLUSIONS AND BENEFIT RISK

Merional has been licensed for clinical use since 1991 and was first licensed in UK since 2002 via the intramuscular route. The need to improve patient compliance and comfort and reduce the need to involve health care professionals has led to the current application for use via the sc route of administration. Notably, it is already licensed for sc use in all but 3 countries.

Two clinical studies involving the pharmacokinetics as well as an efficacy study have been submitted in support of the application.

The PK study did not show formal evidence of bioequivalence with respect to the primary endpoint, since the sc and the i.m. route of administration showed statistical differences with respect to both AUC and C_max although the 90% CI was still within the acceptance range and appeared to be bioequivalent for AUC. With respect to C_max of FSH, the 90% CI was outside the bioequivalence confidence intervals, albeit, by 2%. The PK parameters for LH which was the secondary endpoints were both outside the bioequivalence confidence intervals.

It is appreciated that there are design issues for bioequivalence studies due to the presence of endogenous hormones and necessity for baseline adjustment for the same as well as the inability to fully downregulate FSH and LH production. Although it would be considered appropriate to determine bioequivalence on both components in the product, it should be noted that differences in their biochemical profile can affect bioactivity and degradation. In the case of LH the shorter half life compared to FSH, poses particular problems.

With respect to the efficacy study, the applicant has provided the output from an analysis of variance (ANOVA) including 90% and 95% confidence intervals for the primary endpoint, i.e. difference in the mean number of oocytes in each treatment arm. Results of the analysis of variance (ANOVA) with a 90% CI, shows that the two treatment groups are equivalent in term of mean number of oocytes retrieved. When the same analysis is performed with a 95% CI, the upper confidence limit is outside of the pre-specified limits (i.e. 20% of the mean number of oocytes retrieved in the reference – i.m. group). The 20% equivalence limit used in the study resulted in a definition of equivalence that is considerably more stringent than a definition based on clinical relevance. If an equivalence limit of a clinically relevant difference of 2 oocytes is used, then the equivalence of the formulations has been demonstrated regardless of whether 90% or 95% confidence intervals are used.

In conclusion, it is agreed that lack of bioequivalence itself does not prove lack of clinical benefit. C_max for FSH is not considered relevant and AUC is considered the more important pharmacokinetics parameter which showed bioequivalence for FSH. Clinical data were considered important and it was not possible to provide sufficient evidence of equivalence from pharmacokinetic data alone. It was also considered that FSH levels and measurements, especially after a single dose, were not clinically or biologically relevant.

It was agreed that the results of the PK and the efficacy study would therefore support bioequivalence between the sc and im route of administration for Merional.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The proposed product is identical in all quality aspects to the currently approved product.

NON-CLINICAL
As a line extension application, no non-clinical studies are required and none have been provided. Clinical data are available which obviates the need for bridging studies to assess local tolerance.

The non-clinical sections of the SmPC are identical to those of the licensed product and are acceptable.

EFFICACY AND SAFETY
Although it was not possible to provide sufficient evidence of equivalence from pharmacokinetic data alone, it was agreed that demonstration of clinical benefit would override any objections based on lack of pharmacokinetic bioequivalence.

Hence, the results of the PK and the efficacy study support bioequivalence between the sc and im route of administration for Merional.

The SmPC, PIL and labelling are acceptable.

BENEFIT-RISK ASSESSMENT
No new non-clinical or clinical safety concerns have been identified. Sufficient clinical experience with Merional 75 IU & 150 IU, powder and solvent for solution for injection via the im route is considered to have demonstrated the therapeutic value of the new sc route of administration. The benefit-risk balance is, therefore, considered to be positive.
Merional sc 75 IU & 150 IU, powder and solvent for solution for injection

(menotrophins)

PLs 21039/0016 & 0017

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation application 8th of July 2009
2 Following standard checks the MHRA informed the applicant that its application was considered valid on 27th of July 2009
3 Following assessment of the submitted data, a request for supplementary information was sent to the applicant on 22nd of February 2010
4 The applicant submitted its response to the supplementary information request in a letter dated 24th August 2010
5 Following assessment of the submitted data, a further request for supplementary information was sent to the applicant on 16th December 2010
6 The applicant submitted its response to the supplementary information request in a letter dated 7th March 2011
5 The application was finalised on 2nd August 2011
Merional sc 75 IU & 150 IU, powder and solvent for solution for injection

(menotrophins)

PLs 21039/0016 & 0017

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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</tr>
</tbody>
</table>
Summary of Product Characteristics (SmPC)

Merional sc 75 IU & 150 IU, powder and solvent for solution for injection

(menotrophins)

PLs 21039/0016 & 0017
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Merional sc 75 IU Powder and solvent for solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

Each one ml vial of Merional sc 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 sc 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 sc is indicated for use in adults only

4.2 Posology and method of administration

Treatment with Merional sc 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 sc (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 sc is to develop a single mature Graafian follicle from which the ovum will be released after the administration of hCG Merional sc 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 sc 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 sc 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 sc 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 Merional sc 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 sc 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 sc 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 sc 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 sc and is increased according to the patient’s response. Should an increased dose of Merional sc 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 sc 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 sc 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 sc is intended for 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 sc 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 sc 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 sc 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 sc 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 sc 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 sc 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 sc 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, haemoconcentration, 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 sc 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 sc 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 sc/hCG therapy.

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

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

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

### 4.6 Fertility, pregnancy and lactation

**Pregnancy**
Merional sc 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 sc should not be used during breast-feeding. During lactation the secretion of prolactin can entail a poor response to ovarian stimulation.
4.7 Effects on ability to drive and use machines

Merional sc 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

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\(^{1}\) 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.

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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.

4.9 Overdose

The effect of an overdose of Merional sc 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

Pharmacotherapeutic group Gonadotrophins/human menopausal gonadotrophin
ATC Code G03GA02

Merional sc 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 sc 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 sc 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 incompatibility studies Merional sc 75 IU should be diluted with sodium chloride solution only and must not be mixed with other medicinal products.

6.3 Shelf life

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 with a dark green coloured flip cap

Solvent: 1 ml clear Type I glass ampoule.

**Pack size:**
Carton containing 1 vial of Merional sc 75 IU and 1 ampoule of solvent (1 ml)
Carton containing 10 vials of Merional sc 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 discoloration.
3. Remove the dark green coloured flip cap from the Merional sc 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 sc (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 sc 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 sc 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(S)

PL 21039/0016

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02/08/2011

10 DATE OF REVISION OF THE TEXT

02/08/2011
1 NAME OF THE MEDICINAL PRODUCT

Merional sc 150 IU Powder and solvent for solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

Each one ml vial of Merional sc 150 IU contains:
150 IU Menotrophin BP (Human menopausal gonadotrophin, HMG) providing 150 IU follicle stimulating hormone (FSH) and 150 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 sc 150 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 sc is indicated for use in adults only

4.2 Posology and method of administration

Treatment with Merional sc 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 sc (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 sc is to develop a single mature Graafian follicle from which the ovum will be released after the administration of hCG. Merional sc 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 sc 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 sc 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 sc 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 Merional sc 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 sc 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 sc 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 sc 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 sc and is increased according to the patient's response. Should an increased dose of Merional sc 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 sc 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 sc 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 sc is intended for 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 sc 150 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.

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**Merional sc 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.**

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### 4.3 Contraindications

Merional sc 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 sc 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 sc 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 sc 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 sc 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, haemoconcentration, 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 sc 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 sc 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.

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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.

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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 sc/hCG therapy.

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

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

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Pregnancy
Merional sc 150 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 sc should not be used during breast-feeding. During lactation the secretion of prolactin can entail a poor response to ovarian stimulation.
Fertility
Merional sc 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 sc 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.

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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.

4.9 Overdose

The effect of an overdose of Merional sc 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.

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In men deficient in FSH, Merional sc 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 gonadotrophin, 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 sc 150 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 incompatibility studies Merional sc 150 IU should be diluted with sodium chloride solution only and must not be mixed with other medicinal products.

6.3 Shelf life

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 with a dark green coloured flip cap
Solvent: 1ml clear Type I glass ampoule.

**Pack size:**
Carton containing 1 vial of Merional sc 150 IU and 1 ampoule of solvent (1 ml)
Carton containing 10 vials of Merional sc 150 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 discoloration.
3. Remove the dark green coloured flip cap from the Merional sc 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 1 ml 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 sc (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 sc 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 sc 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(S)**

PL 21039/0017

9 **DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION**

02/08/2011

10 **DATE OF REVISION OF THE TEXT**

02/08/2011
Patient Information Leaflet

Merional sc 75 IU & 150 IU, powder and solvent for solution for injection (menotrophins)

PLs 21039/0016 & 0017
Merional sc 75 IU and 150 IU powder and solvent for solution for injection

Menotrophin

Menotrophin belongs to a group of medicines called sex hormones or gonadotropins.

Benefits of using Menotrophin sc

Menotrophin is used to stimulate the reproductive organs in both males and females, whether naturally or not. Menotrophin is used to treat infertility in women and men in the following situations:

- Women who are not producing (producing) eggs who have not responded to clomiphene citrate or other similar medicine
- Women having treatment to stimulate their ovaries to produce eggs in assisted conception procedures such as in vitro fertilization (IVF)
- Men who have little or no sperm production due to very low hormone levels.

Merional sc is a preparation of a medicine called menotrophin.

Merional sc is a powder and solvent for solution for injection.

Merional sc is presented as a powder in a vial and is a solvent in an ampoule.

Risks of using Merional sc

- Becoming pregnant while using Merional sc due to non-menometrical use.
- A risk of overdose in the ovary (ovarian hyperstimulation or OHSS) will become more severe or prolonged if pregnancy occurs.
- There is an increased chance of multiple births (more than one baby).
- With sex, there is a higher risk of problems for the mother during the pregnancy and at or around the time of birth.
- The chances of miscarriage are higher than usual in those with other fertility treatments.
- There is a slightly higher risk of an ovarian (causing risk) pregnancy, pregnancy outside the womb (ectopic pregnancy), particularly if you have a history of damaged fallopian tubes.
- There are signs of ovarian and other reproductive system tumours in women having infertility treatment.
- There may be a slightly higher risk of an ovarian (causing risk) pregnancy, pregnancy outside the womb (ectopic pregnancy), particularly if you have a history of damaged fallopian tubes.
- You have been advised to stop treatment for any reason.
- You and your close family members have been advised to stop treatment.
- You have a history of bleeding or damaged fallopian tubes (tubal disease).

Tell your doctor if you are taking any of the following medicines.

Your doctor may give you other medicines as part of your fertility treatment.

These medicines may have an effect on Merional sc. If you have any further questions about these medicines, ask your doctor.

Tell your doctor if you are taking any other medicine, including medicines obtained without a prescription.

Pregnancy and breast-feeding

Do not use Merional sc if you are pregnant or breast-feeding.

Important information about some of the ingredients of Merional sc.

This medicine contains salmon made up in 1 ml of fluid less than 1 ml of sodium (23 mg). This is an essential sodium.

Medical checks before your treatment

Your doctor will check your:
- Fertility and the effect of any previous fertility treatment.
- Thyroid and adrenal glands are working properly.
- You do not have tumours of the pituitary gland (pituitary tumours) or hyperthyroidism.
- You do not have high prolactin levels in the blood.
- Your prolactin levels are low.

Your sperm analysis includes sperm count.

3. How to use Merional sc

Always use Merional sc exactly as your doctor has shown you.

Your medicine can be given to you by a doctor or a qualified healthcare professional. You may be able to administer this medicine yourself.

Important:

Your doctor will choose the dose that is right for you.

Your dose will be shown clearly on the label on your pharmacist's pack. If you do not get, you are not sure, ask your doctor or pharmacist.

Remember: Merional sc should only be used for the treatment of infertility under the supervision of a doctor or nurse.

How much Merional sc to use

- Women not ovulating and who have not responded to clomiphene citrate or a similar medicine.
- Men with little or no sperm production due to very low hormone levels.

The usual dose is 75-150 IU per day.

Your doctor may change your dose depending on how you have responded.

The maximum daily dose is usually 225 IU per day.

If your doctor cannot see a response after 4 weeks of treatment, your treatment cycle will probably be stopped and restarted at a higher dose.

When your follicles are at the correct size for ovulation to be induced, a single injection of another medicine called hCG (human chorionic gonadotropin) is given. hCG will usually be given within 36 hours to 48 hours after your last Merional sc injection and will ensure that you ovulate approximately 36 hours later. You should have sexual intercourse the day hCG is given and again on the following day. Alternatively, your doctor will advise you on artificial insemination procedures.

If you have too great a response treatment will be stopped and hCG will not be given (see Possible side effects).

For the following cycle, your doctor will prescribe a lower starting dose.

Women having treatment to stimulate their ovaries to produce eggs in assisted conception procedures such as IVF

The usual dose is 150-225 IU per day, starting on days 2 or 3 of the menstrual cycle.

The maximum daily dose is usually 450 IU.

Development of several follicles containing eggs is usually achieved by the tenth day of treatment. Although this can happen anytime from 2-4 days. A single injection of another medicine (human chorionic gonadotropin or hCG) is usually given 24-48 hours after your last Merional sc injection to complete the maturation of the eggs and allow them to be collected for the IVF procedure. This will normally occur 28-36 hours after the hCG injection.

If you have too great a response treatment will be stopped and hCG will not be given (see Possible side effects).

For the following cycle, your doctor will prescribe a lower starting dose.
4. Mix who have little or no sperm production:
The usual dose is 75–150 g given 3–5 times per week.
Your doctor will start your treatment with injections of another medicine called human menopausal gonadotropin (hMG) followed by injections of Menopur. You will need to have Menopur for at least 3 months before any increase in sperm count can be expected. Your doctor may continue your treatment for at least 18 months to maintain satisfactory levels of sperm.

5. Medical setbacks during your treatment:
When you are taking this medicine, your doctor or nurse will be measuring how well your body is responding. This is to make sure that your medicine is working properly and that the dose you are taking is right for you. Your body’s response could be measured in different ways, including:
- Scoring the ovaries using an ultrasound to see the number and size of the follicles (cysts) containing the eggs that are developing
- Measuring the levels of hormones such as estradiol in blood or urine
- Sperm counts.

It is very important that you are closely monitored during treatment with Menopur sc and your doctor will decide on the most appropriate way for you.

What you need to administer Menopur sc:
- One syringe
- One large needle (for mixing the liquid with the powder)
- Two clean syringes
- Two sets of the used needles and glass containers

6. Preparing your injection:
1. It is important to keep everything as clean as possible, so cover your work area and do not use the same needle for different injections.
2. Choose a clean area and set all the items that are needed for injecting the appropriate number of containers of powder and solvent required for the dose your doctor has chosen for you.

Each Menopur 75 IU contains 75 IU of Menotrophin A and Menopur 150 IU contains 150 IU of Menotrophin A.

Ask your pharmacist for a needle of 1 ml of solvent.

7. Attach the large needle to the end of the syringe, leaving the solvent cover in place.
8. Carefully break the top of the solvent container. If it breaks, the solvent will leak. Remove solvent cover. Withdraw all the liquid from the syringe with the large needle and a syringe. Arrange syringe and needle so that they will both be ready to touch the needle. Remove cover or needle.

9. Insert needle up to a depth of 2 cm into a clean spot on the abdomen or thigh.
10. Push the needle down halfway, making sure the needle is completely inserted, adding any air bubble in the needle by pulling back on the plunger. Push the complete plunger in the needle and hold for 10 seconds. Do not touch the needle.

11. Place the needle and the solvent into the syringe and check for excess air in the syringe. Place a small amount of solvent on the needle and wipe it with a cotton bud.

12. Take immediate medical help if you have any of these symptoms:
- Sensing of the ovaries (long brown or red masses)
- Severe fever and shivering
- Breathing difficulties
- Severe pain in the abdomen
- Bleeding
- Nausea

6. Further information:
What Menopur sc contains:
The active substance is menotrophin A. Each 75 IU contains of powder with 75 IU of follitropin alpha and 15 IU of luteinising hormone. Each 150 IU contains of powder with 150 IU of follitropin alpha. It also contains 75 IU of luteinising hormone.

The other ingredients in the powder are:
- Lactose monohydrate
- The solvent contains 1 ml of saline (sodium chloride 0.9% w/v) solution.

What Menopur sc looks like:
Menopur sc is supplied as a powder and a solvent for solution for injection.

The powder is white and comes in a small glass container (vial). The solvent is a colourless solution that comes in a small glass container (amphoule).

Menopur sc is contained in a container containing 75 IU of powder and 1 ampoule of solvent in 10 ml of powder and 15 ampoules of solvent. Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Baxter SRL, Via M. de Casabianca 2, 20900 Milan, Italy

Manufacturer:
Bayer Schering Pharma S.A., 4102 Cubs (Switzerland)

Batched in the UK by:
Elastra Pharmaceuticals Limited, 29 Westport Manor, Long Eaton, Derby, DE7 6EB. Baxter UK Ltd.

This leaflet was last updated on 13 August 2010.
Labelling

Merional sc 75 IU & 150 IU, powder and solvent for solution for injection

(menotrophins)

PLs 21039/0016 & 0017
Merional sc 75 IU
(Menetropin BP)
For subcutaneous use.
Discard remaining solution after use.

IBSA Institut Biocimique SA
Pellicoli di proprietà IBSA
da rimanere a lavoro ultimo
Ogni manomissione è vietata

Dimensione etichetta 25 x 40 mm

Solvent: Sodium chloride 0.9% • 1ml

Lot.: 
Exp.: 

Colori:
Nero
Blu 294
Rossa 7425
Verde 369
Bianco in retro
Merional sc 150 IU

Merional sc 150 IU
Powder and solvent for solution for injection
(Menotrophin BP)
Human Menopausal Gonadotrophin (HMG)

For indications and method of use, refer to the package leaflet enclosed.

Product licence number: NMC2602017

Product licensor holder: BSA Pharmaceuticals India Ltd.
VIA Martiri di Cenobritto 7, 20046 (L) Italy

Distributor in UK: PMS International Ltd.,
24 Westferry Drive, Eastleigh, Hampshire.
SO30 3DL, UK.

Composition (g/ml): Final preparation of Menotrophin BP 150 IU/ml, that is containing 150 IU L-hCG activity, inactive mannitol, preservative (phenylmercuric borate) and water for injection.

For subcutaneous injection. The vial should be used immediately after injection. Do not store above 25°C. Shake well before use. Discard any unused contents in this original pack. Keep out of the reach and sight of children.