

**Menopur 150 IU
Powder and solvent for solution for injection**

(menotrophin)

PL 03194/0109

UKPAR

TABLE OF CONTENTS

Lay summary	P2
Scientific discussion	P3
Steps taken for assessment	P23
Steps taken after assessment	P24
Summary of product characteristics	P25
Product information leaflet	P36
Labelling	P39

Menopur 150 IU
Powder and solvent for solution for injection
(menotrophin)
PL 03194/0109

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Ferring Pharmaceuticals Limited a Marketing Authorisation for the medicinal products Menopur 150 IU powder and solvent for solution for injection (PL 03194/0109) on 21st September 2011. This application was submitted as a standard abridged national application in accordance with Article 8(3), known active substance, of Directive 2001/83/EC. This application is a line extension of Menopur 75 IU powder and solvent for solution for injection (PL 03194/0074).

This medicine is subject to restricted medical prescription and is indicated for treatment of female and male infertility in the following groups of patients:

- Anovulatory women: Menopur can be used to stimulate follicle development in amenorrhoeic patients. Clomiphene (or a similar ovulation inducing agent which influences steroid feed-back mechanisms) is the preferred treatment for women with a variety of menstrual cycle disturbances, including luteal phase insufficiency with anovulatory cycles and with normal prolactin, and also amenorrhoeic patients with evidence of endogenous oestrogen production but normal prolactin and normal gonadotrophin levels. Non-responders may then be selected for menotrophin therapy.
- Women undergoing superovulation within a medically assisted fertilisation programme: Menopur can be used to induce multiple follicular development in patients undergoing an assisted conception technique such as in-vitro fertilisation (IVF).
- Hypogonadotrophic hypogonadism in men: Menopur may be given in combination with human chorionic gonadotrophin (e.g. Choragon) for the stimulation of spermatogenesis. Patients with primary testicular failure are usually unresponsive.

A critical review of the non-clinical and clinical data presented to the MHRA demonstrated that Menopur is effective for the treatment of female and male infertility in the specified groups of patients. No new safety risks were identified and the safety profile of Menopur was considered to be acceptable. It was therefore judged that the benefits of using this product outweigh the risks, hence the application has been granted.

Menopur 150 IU
Powder and solvent for solution for injection
(menotrophin)
PL 03194/0109

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction	P4
Pharmaceutical assessment	P5
Pre-clinical assessment	P15
Clinical assessment	P17
Overall conclusions and risk benefit assessment	P22

INTRODUCTION

Based on the review of data on safety and efficacy the UK granted a Marketing Authorisation to Ferring Pharmaceuticals Limited for the medicinal product Menopur 150 IU powder and solvent for solution for injection (PL 03194/0109) on 21st September 2011. This application was submitted as a standard abridged national application in accordance with Article 8(3), known active substance, of Directive 2001/83/EC. This application is a line extension of Menopur 75 IU powder and solvent for solution for injection (PL 03194/0074).

This medicine is subject to restricted medical prescription and is indicated for treatment of female and male infertility in the following groups of patients:

- Anovulatory women: Menopur can be used to stimulate follicle development in amenorrhoeic patients. Clomiphene (or a similar ovulation inducing agent which influences steroid feed-back mechanisms) is the preferred treatment for women with a variety of menstrual cycle disturbances, including luteal phase insufficiency with anovulatory cycles and with normal prolactin, and also amenorrhoeic patients with evidence of endogenous oestrogen production but normal prolactin and normal gonadotrophin levels. Non-responders may then be selected for menotrophin therapy.
- Women undergoing superovulation within a medically assisted fertilisation programme: Menopur can be used to induce multiple follicular development in patients undergoing an assisted conception technique such as in-vitro fertilisation (IVF).
- Hypogonadotrophic hypogonadism in men: Menopur may be given in combination with human chorionic gonadotrophin (e.g. Choragon) for the stimulation of spermatogenesis. Patients with primary testicular failure are usually unresponsive.

Menopur 150 IU powder and solvent for solution for injection contains lyophilised powder of highly purified Menotrophin (HP hMG) and is reconstituted with the solvent provided prior to use. Menopur 150 IU contains HP hMG corresponding to follicle stimulating hormone activity (FSH) 150 IU and luteinizing hormone activity (LH) 150 IU. HP-hMG is an almost white or slightly yellow powder containing not less than 2000 IU of FSH and LH bioactivity per mg substance, and is soluble in water.

Menopur powder is available in a 2 ml glass (Type I) vial with rubber (halobutyl type I) stopper closed with a flip off seal. The solvent is available in a 1 ml glass (Type I) ampoule. The product is supplied in packs of 5 or 10 vials with the corresponding number of solvent ampoules.

The original licence for Menopur 75 IU powder and solvent for solution for injection (PL 03194/0074) was granted on 19th November 1999 and this subsequent line extension to add a new strength (150 IU) was granted on 21st September 2011.

QUALITY ASSESSMENT

1 REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORISATION

N/A

2 INTRODUCTION

Menopur 150 IU powder and solvent for solution for injection contains lyophilised powder of highly purified Menotrophin (HP hMG) and is reconstituted with the solvent provided prior to use. Menopur 150 IU contains HP hMG corresponding to follicle stimulating hormone activity (FSH) 150 IU and luteinizing hormone activity (LH) 150 IU.

Menopur is produced from the urine of post menopausal women. Human Chorionic Gonadotrophin (hCG), a naturally occurring hormone in postmenopausal urine, is present in Menopur and contributes to the overall luteinizing hormone (LH) activity. Menopur 150 IU lyophilised powder contains HP hMG and excipients (lactose monohydrate, polysorbate 20, sodium phosphate dibasic heptahydrate and phosphoric acid). The provided solvent for reconstitution contains excipients (metacresol and water for injection).

HP hMG belongs to the pharmacotherapeutic group of gonadotrophins (ATC code: G03G A02). HP hMG, which contains both FSH and LH activity, stimulates ovarian follicular growth and development as well as gonadal steroid production in women who do not have primary ovarian failure. Treatment with Menopur is usually followed by administration of hCG to induce final follicular maturation and ovulation.

2.1 Legal basis

Submitted in accordance with Directive 2001/83/EC; Article 8(3): known active substance

This is a line extension: change or addition of a new strength/potency.

The applicant holds a market authorisation for Menopur 75 IU Powder and Solvent for Solution for Injection. This is a National UK license (PL 03194/0074)

2.2 Use

Menopur is indicated for the treatment of female infertility in the following clinical situations:

- Anovulation, including polycystic ovarian disease (PCOD), in women who have been unresponsive to treatment with clomiphene citrate.
- Controlled ovarian hyperstimulation to induce the development of multiple follicles for assisted reproductive technologies (ART) (e.g. in vitro fertilisation/embryo transfer (IVF/ET), gamete intra-fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)).
- Hypogonadotrophic hypogonadism in men.

It is intended for subcutaneous or intramuscular injection

2.3 Scientific advice

N/A

2.4 Legal status

POM

3. DRUG SUBSTANCE

3.1 General information

3.1.1 Nomenclature

The following names are used to identify gonadotrophins obtained from the urine of post-menopausal women having FSH and LH activity:

INN/BP: Menotrophin

USP: Menotropins

Other non-proprietary names: human Menopausal Gonadotrophin (hMG)

3.1.2 Structure

LH, hCG and FSH belong to the same family of glycoprotein hormones. The molecules are heterodimers composed of an alpha and a beta subunit held together by ionic and hydrophobic forces. While the alpha-subunit is common for these three gonadotropins, the beta-subunits are unique, giving them their different biological characteristics.

The alpha-subunit contains 92 amino-acids (aa) and two N-linked glycosylation sites at aa 52 and 78.

The beta-subunit of hCG contains 145 aa and two N-linked (Asn₁₃ and Asn₃₀) and 4 O-linked glycosylation sites localised on the 25- to 30- aa carboxy-terminal extension.

The beta-subunit of FSH contains 111 aa and two N-linked glycosylation sites (Asn₇ and Asn₂₄), while LH contains 121 aa and a single N-linked glycosylation site at Asn₃₀.

The carbohydrate side chains on the subunits are highly heterogeneous, thus multiple isoforms of each glycoprotein exist.

3.1.3 General properties

HP-hMG is an almost white or slightly yellow powder containing not less than 2000 IU of FSH and LH bioactivity per mg substance, and is soluble in water.

3.2 MANUFACTURE

3.2.1 Manufacturers

The applicant has provided full details of drug substance manufacturers and QC testing sites. The MAH has provided current Good Manufacturing Practice (GMP) certificates from the relevant competent supervising authorities for all manufacturing sites.

3.2.2 Manufacturing process

Urine is collected from postmenopausal women in Argentina and purified to obtain the final drug substance (hMG-HP). The applicant has provided satisfactory information regarding the extraction/purification of hMG-HP including a flow chart.

In general the manufacturing process is satisfactorily described, including information relating to the filtration materials and sanitation/regeneration procedures for each of the chromatography columns.

3.2.3 Control of materials

Starting materials (Urine)

Urine is donated on a voluntary basis, with no incentives i.e. payment. Each donor is interviewed and asked to fill in a general health questionnaire (translated version included in the dossier) relating to addiction (drug/alcohol); infection (i.e. hepatitis, HIV), age, medication received, travel to UK/Ireland. Approved donors can withdraw at any time.

Testing of the collected urine is adequate and satisfactorily described.

Process Materials

The quality of materials used during manufacture is acceptable.

3.2.4 Control of Critical Steps and Intermediates

In process controls are in place, with defined acceptance limits, for FSH activity (potency), yield and moisture content (where drying takes place) for each fraction.

Process related controls for each process step are provided and, in general, there are appropriate process controls in place.

3.2.5 Process Validation

The applicant has provided the summary of a retrospective validation carried on the manufacture of DS. The consistency of the manufacturing process has been adequately demonstrated for each process step.

3.2.6 Manufacturing Process Development

The manufacturing process development has been adequately described.

3.3 CHARACTERISATION

Refer to the introduction for an overall summary of the alpha/beta chain structure and glycosylation sites.

The action of FSH is mediated by a distinct receptor, while LH and hCG exert their actions through the same receptor (McFarland, Sprengel et al. 1989). In addition, the beta-chain of these two glycoproteins have 82% protein sequence homology which makes it difficult to accurately measure the specific content of LH and hCG in menotrophin drug substances.

The applicant has provided an adequate summary of the characterisation methods used and their results.

Table 1. Summary of different molecular forms of LH and hCG isolated from urine

related molecule	Structure
Regular hCG	• α-subunit and β-subunit • Mono- and biantennary N-linked oligosaccharides • O-linked oligosaccharides
Pituitary hCG	• α-subunit and β-subunit • Mono- and biantennary sulfated N-linked oligosaccharides • O-linked oligosaccharides
Free hCG β -subunit	• Only β-subunit present, no α-subunit • Biantennary N-linked oligosaccharides • O-linked oligosaccharides
hCG β -core fragment	• Degraded β-subunit present (β6-40 and β55-92, held together by disulfide linkages), no α-subunit • Degraded biantennary oligosaccharide present • No O-linked oligosaccharides
Regular LH	• α-subunit and β-subunit • Mono- and biantennary N-linked oligosaccharides
LH β -core fragment	• Degraded β-subunit present (β6-40 and β55-92, held together by disulfide linkages), no α-subunit • Degraded biantennary oligosaccharide present,

Given the history of safe use of this product and that it is already licensed, the characterisation of the process and product related impurities of the product is deemed acceptable. It is agreed that the level of ethanol in the final product is well below established safety limits.

3.4 CONTROL OF DRUG SUBSTANCE

3.4.1 Specification

The applicant has provided the drug substance testing strategy and release specifications, which are acceptable.

3.4.2 Analytical Assay Procedures

A summary of the non-compendial assay methods used for release testing have been provided.

3.4.3 Validation of Analytical Assays

All the non-compendial analytical assays have been satisfactorily validated and their respective validation reports were provided.

3.4.4 Batch Analysis

Representative batch release certification for several batches has been provided. All batches comply with the proposed specifications and the data confirm the quality of drug substance manufactured at commercial scale.

3.4.5 Justification of the Specification

Most of the release assays are justified as they comply with British Pharmacopoeia (BP) requirements. The non-BP specifications are justified on the basis of their validation data.

The justifications are considered acceptable.

3.5 REFERENCE STANDARDS OR MATERIALS

Potency

The in-house working reference standards for potency determination are adequately calibrated and a description of the calibration protocol is provided. The current certificate of analysis for the reference material was provided. The 5 year re-test date is acceptable.

Physicochemical

The current certificate of analysis has been provided for the current working standard and is acceptable.

3.6 CONTAINER CLOSURE SYSTEM

Storage of the drug substance has been adequately described and compatibility of the drug substance with the container is assured on the basis of the stability data presented in section 7 of the dossier.

Shipping studies to demonstrate controlled cold chain shipment have been provided and are satisfactory.

3.7 STABILITY

Appropriate stability studies have been undertaken. Batches have been assessed for potency, purity, IEF, water content, pyrogenicity, and microbial content and all stability indicating acceptance criteria were met for all batches.

A post approval commitment, to place one batch of bulk hMG-HP on long-term stability has been provided.

4. DRUG PRODUCT

4.1 DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

Menopur 150 IU is a sterile, lyophilised powder, intended for injection immediately after reconstitution with the co-packaged solvent (saline solution). Detailed composition of the 150 IU presentation has been provided.

4.2 PHARMACEUTICAL DEVELOPMENT

The excipient content is identical to that of the 75IU formulation, the only difference is the amount of menotrophin, as such minimal formulation development has been undertaken, and the MAH has years of experience with this formulation.

As the formulation is the same as the 75 IU presentation, and the active substance constitutes only 0.1% of the final product, the same lyophilisation program was used as that developed for the 75IU product. In addition the container closure is the same size and material, as such there was no process development undertaken for this new presentation.

The compatibility of the product following reconstitution in vials and syringes was evaluated after several hours storage at room temperature and was found to be satisfactory.

4.3 MANUFACTURE

4.3.1 Manufacturer's

Details of the manufacturers and their responsibilities have been provided. Current GMP certificates for all the manufacturers have been provided and are satisfactory.

4.3.2 Batch formula

Batch size and formula are provided and are satisfactory.

4.3.3 Manufacturing process description

The manufacturing process description is minimalistic, but gives an adequate overview of the process.

4.3.4 Control of critical steps and intermediates

The critical steps and the controls in place are considered sufficient to ensure consistency of product.

4.3.5 Process validation

Several full scale batches have been manufactured in order to validate the process.

Compounding and filtration

pH and appearance controls on several batches of compounded bulk solution are provided and are within specification.

Filter validation has been provided and is adequate.

Bioburden results before filtration and after first filtration have been provided and satisfactorily meet specifications.

Filling

Filling homogeneity was validated using full scale batches at the beginning and end of filling. Overall the results confirm homogeneity of fill and all vials met the required specification.

Lyophilisation

Lyophilisation has been validated and is satisfactory. It has been demonstrated that drying is even throughout the lyophiliser.

Stoppering and inspection

As the same container closures are used as that in the 75 IU presentation, repetition of the microbial ingress testing was not carried out. This is acceptable, as the currently licensed presentation gives assurance that microbial safety is not an issue.

Batch analysis

All specifications were met.

4.4 CONTROL OF EXCIPIENTS

The excipients are Ph. Eur compliant.

None of the excipients are of human origin. Lactose monohydrate is derived from bovine milk, and is not consider a TSE relevant material.

4.5 CONTROL OF DRUG PRODUCT

4.5.1 Specifications

Drug product specifications for the 150 IU presentation have been provided and are compliant with the BP.

4.5.2 Analytical Procedures

Pharmacopoeial methods are not described, which is acceptable.

4.5.3 Validation of Analytical Procedures

Validation of the dissolution assay has not been undertaken, which is acceptable given the nature of the assay.

4.5.4 Batch Analysis

The release data for several validation lots were provided and all specifications were met.

4.5.5 Characterisation of impurities

Potential impurities are considered degradation products.

The applicant relies on the characterisation of impurities that has taken place on the drug substance. This approach is considered acceptable.

4.5.6 Justification of the specification

The specifications are justified on the basis of BP requirements for menotrophins for injection and/or current release specifications for the 75IU presentation.

4.6 REFERENCE STANDARDS OR MATERIALS

The same reference for SEC is used as described in section 3.5.

4.7 CONTAINER CLOSURE SYSTEM

The same container closure, in terms of physical properties and size, is used for this presentation and the currently licensed 75 IU presentation. Its suitability as a pharmaceutical packaging material is therefore proven by the 10 year market history of the 75 IU presentation. The information provided confirms the materials of Ph. Eur. compliant, and the product drawings have also been submitted.

4.8 STABILITY

The applicant has provided stability data using the validation lots. Data was provided from stability studies run for 6, 12 and 36 months.

The data support a shelf-life of 3 years for the powder and the solvent.

5. SOLVENT

5.1 DESCRIPTION AND COMPOSITION

The solvent is the same as that licensed for the 75IU presentation, namely 0.9% (w/v) sodium chloride. The composition is provided and is satisfactory.

5.2 PHARMACEUTICAL DEVELOPMENT

The manufacturing process is well established, as is the compatibility of the solvent with the container closure and the suitability of the container closure to prevent microbial

ingress. Furthermore there is a history of safe use of Menopur 75IU with this solvent, as such no pharmaceutical development has been undertaken.

5.3 MANUFACTURE

5.3.1 Manufacturer's

Details of the manufacturers involved in the manufacture of this product and their responsibilities and been provided and are satisfactory. The manufacturer of the solvent is the same as that packaged with the 75IU presentation. A copy of the current GMP certificate for the solvent manufacturer is provided and is acceptable.

5.3.2 Batch formula

The batch size for the production of the solvent for solution for injection has been provided and is satisfactory. The manufacturing formula has also been provided and is satisfactory.

5.3.3 Manufacturing process description

The manufacturing process is a standard procedure for terminally sterilised parenteral solutions. A flow diagram of the manufacturing process has been provided and is satisfactory. The manufacturing description provided is considered adequate.

5.3.4 Control of critical steps and intermediates

The in-process controls in place during manufacture have been described. These ensure the solvent is thoroughly mixed and the fill volume is consistent. Overall the controls in place should ensure a consistent product is manufactured.

5.3.5 Process validation

Retrospective validation of the manufacturing site was carried out using several batches. The release testing results are provided, and all specifications were met for all batches.

The manufacturing process appears to be adequately validated.

5.4 CONTROL OF EXCIPIENTS

5.4.1 Specifications

All excipients (NaCl, HCl, WFI) are Ph. Eur.

5.5 CONTROL OF SOLVENT

5.5.1 Specification

The release specifications for the solvent have been detailed and are adequate.

5.5.2 Analytical assay description

All release tests for the solvent are Ph. Eur. assays therefore no assay description is provided. This is acceptable.

5.5.3 Analytical assay validation

All release tests for the solvent are Ph. Eur. assays therefore no assay validation data has been provided. This is acceptable.

5.5.4 Batch analysis

Batch analysis results for have been provided for consecutive batches. All release specifications are met.

5.5.5 Justification of the specification

The specification is based on the Ph. Eur. monograph for parenterals, the USP monograph for sodium chloride injection, and tests to specifically identify the sodium and chloride ions present. The limits are acceptable.

5.6 REFERENCE STANDARDS

As all of the release assays are Ph. Eur. there are no product specific standards required for testing, as such no additional information is given. This is acceptable.

5.7 CONTAINER CLOSURE

The sodium chloride solution is filled into 1 ml colourless glass ampoules (type 1 glass according to Ph.Eur.).

5.8 STABILITY

Several batches have been placed on long-term and accelerated stability studies.

The results confirm the solvent is stable through out the proposed 36 month shelf-life when not stored above 25°C. The applicant has also committed to place one batch per year on long-term stability. This is acceptable.

6. APPENDICES

6.1 FACILITIES AND EQUIPMENT

No information has been provided in relation to the facilities and equipment. This is acceptable as the manufacturing facilities are the same as for Menopur 75 IU, as such this information has already been assessed, and GMP compliance is demonstrated by the provision of GMP certification.

6.2 ADVENTITIOUS AGENTS SAFETY EVALUATION

6.2.1 Virus Validation of Manufacturing Process

Validation of the manufacturing process in relation to its virus inactivation capacity was carried out in 1994, using the same principles as would be expected today. The data presented confirms the validation of the identified virus removal/inactivation stages of manufacture is compliant with current EU requirements.

6.2.2 Microbial safety

Overall the microbial safety of the drug product is considered satisfactory.

6.3 NOVEL EXCIPIENTS

N/A

7. REGIONAL INFORMATION

7.1 PROCESS VALIDATION SCHEME FOR THE DRUG PRODUCT

N/A

7.2 MEDICAL DEVICE ISSUES

N/A

7.3 TSE ISSUES

EMA/CHMP/BWP/472717/2009 reports on an expert workshop on CJD risk and urine derived products. They concluded that there is no epidemiological evidence of CJD or vCJD transmission by urine derived products, though this was not considered a sufficient basis to confirm the safety of such products. It was recommended that the manufactures undertake an evaluation based on published data on the contribution of their manufacturing process to reduce/eliminate TSE agents.

The applicant has provided a risk assessment of their product in relation to the potential for TSE agents to be present in the starting material, and the potential of their manufacturing process to reduce/eliminate those agents. The results demonstrate that there is a low risk of contaminated donations being introduced to the manufacturing process, and the process itself has at least one step that is effective in the removal of prions. This is considered acceptable.

Assessor's Overall Conclusions

All quality issues have been addressed and this application can be approved.

NON-CLINICAL ASSESSMENT

1. INTRODUCTION

1.1 Type of application and aspects on development

This is a national application for Menopur powder and solvent for solution for injection 150 IU submitted as a line extension to the already licensed Menopur 75 IU powder & solvent for solution for injection under Article 8(3).

The proposed indications are:

Treatment of female and male infertility in the following groups of patients:

- *Anovulatory women: Menopur can be used to stimulate follicle development in amenorrhoeic patients. Clomiphene (or a similar ovulation inducing agent which influences steroid feed-back mechanisms) is the preferred treatment for women with a variety of menstrual cycle disturbances, including luteal phase insufficiency with anovulatory cycles and with normal prolactin, and also amenorrhoeic patients with evidence of endogenous oestrogen production but normal prolactin and normal gonadotrophin levels. Non-responders may then be selected for menotrophin therapy.*
- *Women undergoing superovulation within a medically assisted fertilisation programme: Menopur can be used to induce multiple follicular development in patients undergoing an assisted conception technique such as in-vitro fertilisation (IVF).*
- *Hypogonadotrophic hypogonadism in men: Menopur may be given in combination with human chorionic gonadotrophin (e.g. Choragon) for the stimulation of spermatogenesis. Patients with primary testicular failure are usually unresponsive.*

1.2 GLP aspects

No new non-clinical studies have been submitted in support of this application.

2. 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 preparation. 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.

As with the existing product, Menopur IU will be administered clinically by either the subcutaneous or intramuscular route. No changes have been made to the final formulation of the drug product, as such no concerns relating to local tolerance are raised.

3. SUMMARY OF PRODUCT CHARACTERISTICS

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

4. ASSESSOR'S OVERALL CONCLUSIONS

This application for Menopur powder and solvent for solution for injection 150 IU is a line extension to the approved Menopur powder and solvent for solution for injection 75 IU. The only difference between the two products is the amount of drug substance (150 IU compared to 75 IU), as the excipients are quantitatively and qualitatively the same for both products. As such, no local tolerance concerns are raised and it is considered acceptable to cross-refer to the approved non-clinical documentation for Menopur powder and solvent for solution for injection 75 IU.

The granting of a Marketing Authorisation for Menopur Powder and solvent for solution for injection 150 IU is recommended from a non-clinical perspective.

CLINICAL ASSESSMENT

1. INTRODUCTION

1.1 Type of application and regulatory background

A standard abridged line extension application to Menopur 75 IU powder & solvent for solution for injection (PL 03194/0074).

Product to be authorised:

Menopur 150 IU, powder & solvent for solution for injection – PL 03194/0109.

1.2 Clinical background

The development of Menopur has provided an effective and well tolerated highly purified human urinary menotrophin preparation. The rationale of the development of a new strength, 150 IU, is to provide a product that is more convenient to use when doses higher than 75 IU are requested. Up to three vials of the proposed new formulation can be dissolved in 1 mL solvent, thus providing the maximum daily dose in one injection, thereby minimising the inevitable stress and discomfort of injection for the patient.

Assessor's comment: The reduction in the number of vials needed for those who require doses higher than 75 IU is regarded as a benefit.

1.3 Indications

Anovulation (including polycystic ovarian disease (PCOD) in women who have been unresponsive to treatment with clomiphene citrate

WHO group II anovulation refers to women with a variety of menstrual cycle disturbances (including amenorrhea) who exhibit distinct endogenous oestrogen activity, whose gonadotrophin levels are in the normal range, and who may also have fairly regular menstrual bleedings (i.e. less than 35 days apart) but without ovulation.

Anovulatory women belonging to the WHO group II classification are mainly women with polycystic ovarian disease (PCOD) and for these patients clomiphene citrate is being used as first line treatment. Approximately 70–75% of the women ovulate after clomiphene citrate therapy and 30–40% will conceive within six clomiphene citrate treatment cycles. Gonadotrophin treatment has proven effective in WHO group II patients and is proposed for ovulation induction in women failing to ovulate or conceive on clomiphene citrate.

Controlled ovarian hyperstimulation to induce the development of multiple follicles for assisted reproductive technologies (ART) (e.g. in vitro fertilisation/embryo transfer (IVF/ET), gamete intra-fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI))

Assisted reproductive technologies (ART), in particular *in vitro* fertilization (IVF), have improved the success rates in women with tubal disease, couples with unexplained infertility, and anovulatory patients who failed to get pregnant during ovulation induction treatment. Controlled ovarian hyperstimulation with gonadotrophin preparations is used to induce multiple follicle development, allowing more preovulatory follicles to be available at the time of oocyte retrieval for ART.

1.4 Dose and dose regimen

Menopur 150 IU is intended for subcutaneous or intramuscular injection after reconstitution with the solvent provided. Each vial of Menopur consists of a sterile lyophilised powder containing highly purified menotrophin and excipients (lactose monohydrate, polysorbate 20, sodium hydroxide and hydrochloric acid) which after reconstitution with sodium chloride solvent delivers 150 IU of FSH and LH activity. The formulation is a standard formulation. The only difference compared to the already marketed Menopur 75 IU is the amount of the drug substance.

1.5 GCP aspects

No clinical data was presented with this abridged line extension application.

1.6 Orphan medicinal products

N/A

1.7 Paediatric development programme

N/A

1.8 Scientific advice

N/A

1.9 Legal status

POM

2. CLINICAL PHARMACOLOGY

2.1 Pharmacokinetics

Based on a previous bioequivalence study with Menopur 75 IU and 1200 IU, it was concluded that the two formulations were bioequivalent. The rate limiting step in the vascular absorption of FSH is concluded to be the lymphatic flow rate and transportation of FSH, and not concentration driven diffusion from the site of injection to the lymph capillaries. Consequently, it is highly unlikely that the very small difference in concentration in the current 150 IU formulation compared to the marketed 75 IU formulation will have any impact on the overall absorption rate into the vascular system and the expected bioequivalence of the two formulations.

Assessor's comment: There is no clinical data accompanying this line extension. The bioequivalence study has been assessed in an ongoing procedure and is deemed satisfactory.

2.2 Pharmacodynamics

Follicle size and oestradiol levels are well established pharmacodynamic markers of gonadotrophin treatment. The impact of Menopur treatment on these markers has been described for downregulated women undergoing COH for IVF/ICSI in the Clinical Expert Report and in the Clinical Overview for follicle induction in anovulatory women who are unresponsive to clomiphene citrate.

Assessor's comment: No new data was provided with this abridged application. This is acceptable as this line extension involves an increased vial size only.

3. CLINICAL EFFICACY

3.1 Overview of efficacy

The efficacy of Menopur for treatment of women with WHO group II anovulatory infertility who previously had failed to ovulate or conceive on clomiphene citrate, and the efficacy of Menopur for multiple ovarian follicular development in patients undergoing ART was described in the Clinical Overview of 2008.

Assessor's comment: No new data was provided with this abridged application. This is acceptable as this line extension involves an increased vial size only.

4. CLINICAL SAFETY

4.1 Overview of safety

Literature

The literature describing the risks associated with Menopur and other preparations in this pharmacological class was reviewed in the Clinical Expert Report of 2002 and the Clinical Overview of 2005.

Assessor's comment: No new data was provided with this abridged application. This is acceptable as this line extension involves an increased vial size only.

5. POST MARKETING EXPERIENCE

5.1 Postmarketing experience

Menopur was first approved in Denmark on 18 November 1999. As of 31 December 2008 Menopur was approved in 85 countries worldwide. The cumulative exposure to Menopur from 18 November 1999 to 31 December 2008 is estimated to 1,126,212 treatment cycles, corresponding to 450,484 patients. A safety database is maintained at the Pharmacovigilance department at Ferring Pharmaceuticals A/S comprising all adverse events cases reported spontaneously by healthcare professionals, consumers, regulatory authorities, from the scientific literature and serious adverse events occurring in clinical trials (development trials, local phase IV trials, investigator-initiated trials). The cases from the clinical trials included in the development of Menopur have been discussed either in the Clinical Expert Report issued for the ART indication in 2002 or in the Clinical Overview issued in 2005.

As of 31 December 2008, Ferring Global Pharmacovigilance has registered 294 cases of adverse events following treatment with Menopur. A total of 183 cases have been assessed as related to Menopur from first launch in November 1999 to 31 December 2008 (Table 1). In addition to the listed events, 50 cases of ineffective treatment were reported.

Table 1. All adverse drug reactions reported post-marketing

Serious, expected	Serious, unexpected	Non-serious, unexpected	Non-serious, expected
Anaphylactic reaction (1)	Abortion induced (1)	Alopecia (1)	Abdominal discomfort (3)
Adnexa uteri pain (1)	Abortion spontaneous (4) (c2)	Amenorrhoea (1) (c1)	Abdominal distension (9) (c4)
OHSS (62)	Aggression (1) (c1)	Arthralgia (3)	Abdominal pain (4) (c1)
Pulmonary embolism (1)†	Anaphylactic shock (1)	Asthenia (4) ^{VI} (c2)	Allergic reaction (2)
Venous thrombosis (3) ^I	Atrial flutter (1)	Dizziness (4) (c1)	Ascites (1)
	Breast cancer (1)	Gait disturbance (1)	Breast tenderness (3) (c1)
	Capillary leak syndrome (1) ^{IX}	Hepatic enzyme increased (2)	Breast discomfort (2) (c2)
	Cardio-respiratory arrest (1) ^{IX}	Hepatic disorder (2)	Constipation (1) (c1)
	Carotid Thrombosis (1)	Injection site Haemorrhage (2) (c1)	Diarrhoea (3)
	Catastrophic antiphospholipid syndrome (1) ^{II,III}	Irritability (1) (c1)	Dyspnoea (1) (c1)
	Cholestasis of pregnancy (2)	Insomnia (1) (c1)	Headache (4)
	Compartment syndrome (1) ^{IX}	Hemiparesis (1)	Injection site pain (3) (c1)
	Depression (1) (c1)	Malaise (3) (c1)	Injection site reaction (9) (c2)
	Embolism (1)	Micturition urgency (1) (c1)	Pelvic discomfort (1)
	Extrasystoles (1)	Migraine (1) (c1)	Multiple pregnancy (1)
	Hypertension (2) (c1)	Muscle spasms (1)	Nausea (6) (c3)
	Hypothyroidism (1) ^{II}	Oedema peripheral (1)	Rash (7)
	Multiple organ failure (1) ^{IV} †	Ovarian disorder (4) ^{VII} (c3)	Rash pruritic (2)
	Ovarian cancer (1)	Pain (3) (c1)	Skin reactions (1)
	Stomatitis necrotising (1) ^V	Palpitations (2) (c1)	Vomiting (1)
	Simple partial seizures (1)	Photospasm (1)	Weight increased (2) (c1)
		Pyrexia (3)	Urticaria (2)
		Pruritus (2)	
		Vertigo (1) ^{VIII}	
		Vestibular neuronitis (1)	
		Visual disturbance (2)	
		Vitreous floaters (1)	
		Uterine Haemorrhage (1)	

(n) = number of reports; (cn) = number of consumer reports

^I Venous thrombosis includes 1 cases of deep vein thrombosis, one cases of Jugular vein thrombosis, one case of venous thrombosis^{II} Literature case^{III} Simultaneously with OHSS^{IV} Multiple organ failure simultaneously with OHSS^V Limited information^{VI} Asthenia also including fatigue^{VII} Relevant confounding factor^{VIII} This includes balance disorder^{IX} One report includes compartment syndrome, capillary leak syndrome and cardio-respiratory arrest

† Case with fatal outcome

5.2 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.

6. PRODUCT LITERATURE

6.1 SPC & PIL

The SPC and PIL are satisfactory and no clinical changes are requested.

7. OVERALL CONCLUSIONS AND BENEFIT RISK

The general benefits and risks of Menopur in the treatment of anovulatory women who have been unresponsive to clomiphene citrate, and the managing of infertile women undergoing COH to induce multiple follicle development for ART were extensively discussed in the Clinical Overview of 2005 and the Clinical Expert Report of 2002, respectively, and will not be repeated here. It was concluded that Menopur is a well tolerated and effective product in both indications. Seen in a perspective of cumulative experience and total exposure to Menopur, the safety profile is in line with the information stated in the Summary of Product Characteristics. The only difference between the 150 IU product and the marketed 75 IU product is the amount of drug substance, which in the new formulation allows the maximum daily dose to be administered in only one injection. With respect to the bioavailability of the protein components of Menopur, the information available from the clinical studies and the literature do not support that the small difference in concentration would have any consequences on the bioavailability. On the contrary, the available data regarding absorption of proteins such as FSH and LH suggest that the bioavailability is more or less independent of the formulation used. It is therefore concluded that a bioequivalence study is not justifiable.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT**QUALITY**

The important quality characteristics of Menopur 150 IU powder and solvent for solution for injection are well defined and controlled. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

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 non-clinical studies provided to investigate the tolerance of Menopur in the new formulation are satisfactory.

EFFICACY AND SAFETY

The benefit of the new strength, 150 IU, is to provide a product that is more convenient to use when doses higher than 75 IU are requested. Up to three vials of the proposed new formulation can be dissolved in 1 ml solvent, thus providing the maximum daily dose in one injection, thereby minimising the inevitable stress and discomfort of injection for the patient. No new efficacy or safety studies were conducted which is acceptable.

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 Menopur 75 IU powder and solvent for solution for injection is considered to have demonstrated the therapeutic value of Menopur 150 IU powder and solvent for solution for injection. The benefit-risk balance is, therefore, considered to be positive.

Menopur 150 IU
Powder and solvent for solution for injection
(menotrophin)
PL 03194/0109

STEPS TAKEN FOR ASSESSMENT

- 1 The MHRA received the marketing authorisation application on 18th September 2009
- 2 Following standard checks the MHRA informed the applicant that its application was considered valid on 9th February 2010
- 3 Following assessment of the submitted data, a request for supplementary information was sent to the applicant on 15th June 2010
- 4 The applicant submitted its response to the supplementary information request in a letter dated 16th January 2011
- 5 Following assessment of the submitted data, a further request for supplementary information was sent to the applicant on 11th March 2011
- 6 The applicant submitted its response to the supplementary information request in a letter dated 7th July 2011
- 7 The application was finalised on 21st September 2011

Menopur 150 IU
Powder and solvent for solution for injection
(menotrophin)
PL 03194/0109

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

Summary of Product Characteristics

**Menopur 150 IU
Powder and solvent for solution for injection**

(menotrophin)

PL 03194/0109

1 NAME OF THE MEDICINAL PRODUCT

MENOPUR 150 IU powder and solvent for solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial with powder contains highly purified menotrophin (human menopausal gonadotrophin, HMG) corresponding to 150 IU human follicle stimulating hormone activity (FSH) and 150 IU human luteinizing hormone activity (LH).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Appearance of powder: white to off-white lyophilised cake.

Appearance of solvent: clear colourless solution.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications**

Treatment of female and male infertility in the following groups of patients:

- Anovulatory women: MENOPUR can be used to stimulate follicle development in amenorrhoeic patients. Clomiphene (or a similar ovulation inducing agent which influences steroid feed-back mechanisms) is the preferred treatment for women with a variety of menstrual cycle disturbances, including luteal phase insufficiency with anovulatory cycles and with normal prolactin, and also amenorrhoeic patients with evidence of endogenous oestrogen production but normal prolactin and normal gonadotrophin levels. Non-responders may then be selected for menotrophin therapy.
- Women undergoing superovulation within a medically assisted fertilisation programme: MENOPUR can be used to induce multiple follicular development in patients undergoing an assisted conception technique such as in-vitro fertilisation (IVF).
- Hypogonadotrophic hypogonadism in men: MENOPUR may be given in combination with human chorionic gonadotrophin (e.g. Choragon) for the stimulation of spermatogenesis. Patients with primary testicular failure are usually unresponsive.

4.2 Posology and method of administrationAnovulatory infertility:

Menotrophin is administered to induce follicular maturation and is followed by treatment with chorionic gonadotrophin to stimulate ovulation and corpus luteum formation.

The dosage and schedule of treatment must be determined according to the needs of each patient. Response is monitored by studying the patient's urinary oestrogen excretion or by ultrasound visualisation of follicles. Menotrophin may

be given daily by either intramuscular or subcutaneous injection to provide a dose of 75 to 150 units of FSH and 75 to 150 units of LH, and gradually adjusted if necessary until an adequate response is achieved, followed after 1 or 2 days by chorionic gonadotrophin. In menstruating patients, treatment should be started within the first 7 days of the menstrual cycle. The treatment course should be abandoned if no response is seen in 3 weeks. This treatment cycle may be repeated at least twice more if necessary. Alternatively, three equal doses of menotrophin, each providing 225 to 375 units of FSH with 225 to 375 units of LH, may be given on alternate days followed by chorionic gonadotrophin one week after the first dose.

In the daily therapy schedule, the dose is gradually increased until oestrogen levels start to rise. The effective dose is then maintained until adequate preovulatory oestrogen levels are reached. If oestrogen levels rise too rapidly, the dose should be decreased.

As a measure of follicle maturity the following values can be taken:

- total urinary oestrogen: 75 -150 micrograms (270 – 540 nmol)/24 hours
- plasma 17 beta-oestradiol: 400 -800 picograms/ml (1500 – 3000 pmol/L).

When adequate pre-ovulatory oestrogen levels have been reached, administration of MENOPUR is stopped, and ovulation may then be induced by administering human chorionic gonadotrophin at a dose of 5000 -10000 IU.

Women undergoing superovulation in IVF or other assisted conception techniques:

In in-vitro fertilisation procedures or other assisted conception techniques menotrophin is used in conjunction with chorionic gonadotrophin and sometimes also clomiphene citrate or a gonadorelin agonist. Stimulation of follicular growth is produced by menotrophin in a dose providing 75 to 300 units of FSH with 75 to 300 units of LH daily. Treatment with menotrophin, either alone or in conjunction with clomiphene or a gonadorelin agonist, is continued until an adequate response is obtained and the final injection of menotrophin is followed 1 or 2 days later with up to 10000 units of chorionic gonadotrophin.

Maturation of follicles is monitored by measurement of oestrogen levels, ultrasound and/or clinical evaluation of oestrogen activity. It is recommended there should be at least 3 follicles greater than 17mm in diameter with 17 beta-oestradiol levels of at least 3500 pmol/L (920 picograms/ml). Egg maturation occurs by administration of human chorionic gonadotrophin in a dose of 5000-10000 IU, 30 -40 hours after the last MENOPUR injection. Human chorionic gonadotrophin should not be administered if these criteria have not been met. Egg retrieval is carried out 32 -36 hours after the human chorionic gonadotrophin injection.

Male infertility:

Spermatogenesis is stimulated with chorionic gonadotrophin (1000 – 2000 IU two to three times a week) and then menotrophin is given in a dose of 75 or 150 units of FSH with 75 or 150 units of LH two or three times weekly. Treatment should be continued for at least 3 or 4 months.

Children:

Not recommended for use in children.

Elderly:

Not recommended for use in the elderly.

Method of Administration:

By intramuscular or subcutaneous use.

The dry substance must be reconstituted with the diluent prior to use, see section 6.6 for reconstitution method.

4.3 Contraindications

Men and Women

MENOPUR is contraindicated in men and women with: -Tumours of the pituitary or hypothalamic glands -Hypersensitivity to the active substance or any of the excipients used in the formulation (see section 6.1)

Men

- Tumours in the testes
- Prostate carcinoma

Women -Ovarian, uterine or mammary carcinoma -Pregnancy and lactation - Gynaecological haemorrhage of unknown aetiology -Ovarian cysts or enlarged ovaries not due to polycystic ovarian disease.

In the following situations treatment outcome is unlikely to be favourable, and therefore MENOPUR should not be administered:

- Primary ovarian failure
- Malformation of sexual organs incompatible with pregnancy
- Fibroid tumours of the uterus incompatible with pregnancy
- Structural abnormalities in which a satisfactory outcome cannot be expected, for example, tubal occlusion (unless superovulation is to be induced for IVF), ovarian dysgenesis, absent uterus or premature menopause.

4.4 Special warnings and precautions for use

MENOPUR is a potent gonadotropic substance capable of causing mild to severe adverse reactions, and should only be used by physicians who are thoroughly familiar with infertility problems and their management.

In the treatment of female infertility, ovarian activity should be checked (by ultrasound and plasma 17 beta-oestradiol measurement) prior to MENOPUR administration. During treatment, these tests and urinary oestrogen measurement should be carried out at regular intervals, until stimulation occurs. Close supervision is imperative during treatment. See "posology and administration" for optimum response levels of urinary oestrogen and plasma 17 beta-oestradiol. Values below these ranges may indicate inadequate follicular development.

There is considerable inter-patient variability in response to menotrophin administration, with a poor response to menotrophin in some patients. The lowest effective dose in relation to the treatment objective should be used. The first injection of MENOPUR should be performed under direct medical

supervision.

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 MENOPUR dosage and regimen of administration, and careful monitoring of therapy will minimise the incidence of such events. Acute interpretation of the indices of follicle development and maturation requires a physician who is experienced in the interpretation of the relevant tests.

Ovarian Hyperstimulation Syndrome (OHSS)

OHSS is a medical event distinct from uncomplicated ovarian enlargement. OHSS 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 which can result in an accumulation of fluid in the peritoneal, pleural and rarely, in the pericardial cavities.

The severe form OHSS may be life-threatening and is characterised by large ovarian cysts (prone to rupture), acute abdominal pain, ascites, very often hydrothorax and occasionally thromboembolic phenomena. Other symptoms that may be observed include: abdominal distension, severe ovarian enlargement, weight gain, dyspnoea, oliguria and gastrointestinal symptoms including nausea, vomiting and diarrhoea. Clinical evaluation may reveal hypovolaemia, haemoconcentration, electrolyte imbalances, haemoperitoneum, pleural effusions and acute pulmonary distress.

If urinary oestrogen levels exceed 540 nmol (150 micrograms)/24 hours, or if plasma 17 beta-oestradiol levels exceed 3000 pmol/L (800 picograms/ml), or if there is any steep rise in values, there is an increased risk of hyperstimulation and MENOPUR treatment should be immediately discontinued and human chorionic gonadotrophin withheld. Ultrasound will reveal any excessive follicular development and unintentional hyperstimulation. In the event of hyperstimulation, the patient should refrain from sexual intercourse or to use barrier contraception methods for at least 4 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 the hCG administration.

If during ultrasound, several mature follicles are visualised, human chorionic gonadotrophin should not be given as there is a risk of multiple ovulation and the occurrence of hyperstimulation syndrome.

Adherence to recommended MENOPUR dosage, regimen of administration and careful monitoring of therapy will minimise the incidence of ovarian hyperstimulation and multiple pregnancy (see sections 4.2 and 4.8). Patients undergoing superovulation may be at an increased risk of developing hyperstimulation in view of the excessive oestrogen response and multiple follicular development. 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 seven to ten 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 ART procedures the risk of multiple pregnancy is related mainly to the number of embryos replaced, their quality and the age of the patient.

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 ART procedures 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 treatment. The prevalence of ectopic pregnancy after IVF has been reported to be 2 to 5%, as compared to 1 to 1.5% in the general population.

Reproductive system neoplasms

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 if treatment with gonadotrophins increases the baseline risk of these tumours in infertile women.

Congenital malformation

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

carries an increased risk of thromboembolic events.

4.5 Interaction with other medicinal products and other forms of interaction

No drug/drug interaction studies have been conducted with MENOPUR in humans.

Although there is no controlled clinical experience, it is expected that the concomitant use of MENOPUR and clomiphene citrate may enhance the follicular response. When using GnRH agonist for pituitary desensitization, a higher dose of MENOPUR may be necessary to achieve adequate follicular response.

4.6 Pregnancy and lactation

MENOPUR should not be given during pregnancy or to lactating mothers.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

The most frequently reported adverse drug reactions during treatment with MENOPUR in clinical trials are ovarian hyperstimulation, abdominal pain, headache, enlarged abdomen, inflammation at the injection site, pain at the injection site and nausea, with an incidence rate between 2% and 7%. The table below displays the main adverse drug reactions in women treated with MENOPUR in clinical trials according to body system and frequency.

Body System	Frequency	Adverse Drug Reaction
Central/peripheral nervous system disorders	Common (>1/100 <1/10)	Headache
Gastro-intestinal disorders	Common (>1/100 <1/10)	Abdominal pain, enlarged abdomen, nausea and vomiting
Female reproductive disorders	Common (>1/100 <1/10)	Ovarian hyperstimulation
Application site disorders	Common (>1/100 <1/10)	Inflammation at injection site, pain at injection site
Vascular (extracardiac) disorders	Uncommon (>1/1,000 <1/100)	Deep vein thrombosis

In very rare cases, long term use of menotrophin can lead to the formation of antibodies making treatment ineffectual.

Very rare cases of allergic reactions, localised or generalised, and delayed-type hypersensitivity have been reported after treatment with gonadotrophin containing products.

4.9 Overdose

The acute toxicity of menotrophin has been shown to be very low. However, too high a dosage for more than one day may lead to hyperstimulation, which is categorised as mild, moderate or severe. Symptoms of overdosage usually appear 3 -6 days after treatment with human chorionic gonadotrophin.

Mild hyperstimulation -Symptoms include some abdominal swelling and pain, ovaries enlarged to about 5cm diameter. Therapy -rest; careful observation and symptomatic relief. Ovarian enlargement declines rapidly.

Moderate hyperstimulation -Symptoms include more pronounced abdominal distension and pain, nausea, vomiting, occasional diarrhoea, ovaries enlarged up to 12cm diameter. Therapy -bed rest; close observation especially in the case of conception occurring, to detect any progression to severe hyperstimulation. Pelvic examination of enlarged ovaries should be gentle in order to avoid rupture of the cysts. Symptoms subside spontaneously over 2 -3 weeks.

Severe hyperstimulation -This is a rare but serious complication -symptoms include pronounced abdominal distension and pain, ascites, pleural effusion, decreased blood volume, reduced urine output, electrolyte imbalance and sometimes shock, ovaries enlarge to in excess of 12cm diameter. Therapy hospitalisation; treatment should be conservative and concentrate on restoring blood volume and preventing shock. Acute symptoms subside over several days and ovaries return to normal over 20 -40 days if conception does not occur - symptoms may be prolonged if conception occurs.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Gonadotrophins
ATC code: G03G A02

Menotrophin is a gonadotrophin extracted from the urine of postmenopausal women and having both luteinising hormone and follicle stimulating hormone activity. It is given by intramuscular or subcutaneous injection in the treatment of male and female infertility.

Menotrophin (HMG) directly affects the ovaries and the testes. HMG has a gametropic and steroidogenic effect.

In the ovaries, the FSH-component in HMG induces an increase in the number of growing follicles and stimulates their development. FSH increases the production of oestradiol in the granulosa cells by aromatising androgens that originate in the Theca cells under the influence of the LH-component.

In the testes, FSH induces the transformation of premature to mature Sertoli

cells. It mainly causes the maturation of the seminal canals and the development of the spermatozoa. However, a high concentration of androgens within the testes is necessary and can be attained by a prior treatment using hCG.

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. The maximum serum level of FSH is reached approximately 18 hours after intramuscular injection and 12 hours after subcutaneous injection. After that, the serum level decreases by a half-life of approximately 55 hours following intramuscular administration and 50 hours following subcutaneous administration.

Excretion of HMG, following administration, is predominantly renal.

5.3 Preclinical safety data

Toxic effects caused by HMG are unknown in humans.

There is no evidence of teratogenic, mutagenic or carcinogenic activity of HMG. Antibodies against HMG can be built up in single cases following repeated cyclical administration of HMG, causing the treatment to be ineffectual.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Lactose monohydrate

Polysorbate 20

Sodium hydroxide

Hydrochloric acid (for pH adjustment)

Solvent:

Sodium chloride

Hydrochloric acid (for pH adjustment)

Water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Powder: 3 years

Solvent: 3 years

For immediate and single use following reconstitution.

6.4 Special precautions for storage

Do not store above 25°C. Do not freeze. Store in the original container to protect from light.

6.5 Nature and contents of container

MENOPUR is available in the following containers and pack sizes:

Powder: 2 ml glass (Type I) vial with rubber (halobutyl type I) stopper closed with a flip off seal.

Solvent: 1 ml glass (Type I) ampoule.

The product is supplied in packs of 5 or 10 vials with the corresponding number of solvent ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The reconstituted needle, syringe or hypodermic needle, are not included in the packs, the following are recommended to be used;

For drawing up and mixing: 18 gauge 40 mm long needle and disposable sterile 1ml syringe

For injecting: 30 gauge 16 mm needle (hypodermic needle), for subcutaneous injection.

The powder should only be reconstituted with the solvent provided in the package.

Attach the reconstitution needle to the syringe. Withdraw the entire content from the ampoule with solvent and inject the total contents into the vial containing the powder. The powder should dissolve quickly to a clear solution. If not, roll the vial gently between the hands until the solution is clear. Vigorous shaking should be avoided.

If needed, the solution can be drawn up into the syringe again to transfer it to the next vial with powder until the prescribed dose has been reached. Up to three powder vials can be dissolved with one ampoule of solvent.

When the prescribed dose has been reached, draw up the mixed solution from the vial into the syringe, change to the hypodermic needle and administer immediately.

The reconstituted solution should not be administered if it contains particles or is not clear.

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

7 MARKETING AUTHORISATION HOLDER

Ferring Pharmaceuticals Limited
The Courtyard
Waterside Drive
Langley, Berkshire
SL3 6EZ

8 MARKETING AUTHORISATION NUMBER(S)

PL 03194/0109

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/09/2011

10 DATE OF REVISION OF THE TEXT

21/09/2011

Patient Information Leaflet

**Menopur 150 IU
Powder and solvent for solution for injection**

(menotrophin)

PL 03194/0109



Patient Information

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

In this leaflet:

1. What Menopur is and what it is used for
2. Before you use Menopur
3. How to use Menopur
4. Possible side effects
5. How to store Menopur
6. Further information

1. What Menopur is and what it is used for

What Menopur is

Menopur contains a medicine called Highly Purified Menotrophin. This is a mixture of hormones extracted from the urine of women who have passed the menopause, the mixture is then highly purified.

- The dose of these hormones is given in International Units (IU).
- Each bottle (vial) contains the equivalent of 150 IU of FSH (follicle stimulating hormone) and 150 IU of LH (luteinising hormone).

Menopur helps reproductive organs to work normally in both women and men. A fertility specialist should supervise your treatment.

What Menopur is used for

In women, Menopur is used for:

- Infertility caused by eggs not being produced properly in the ovaries (anovulatory infertility).
It works by helping follicles (which contain eggs) to mature in the ovaries.
- IVF (in vitro fertilisation) and other types of 'assisted conception'.
It works by helping multiple follicles and eggs to develop. The eggs are then harvested and fertilised outside the body.

In men, Menopur is used for:

- Low sperm count (oligospermia).

2. Before you use Menopur

Do not use Menopur if:

- You are allergic (hypersensitive) to menotrophin or any of the other ingredients of Menopur (listed in Section 6).
- You have a tumour in your pituitary gland (a gland located on the base of the brain which produces certain hormones, including growth hormones).
- You have a tumour in a part of your brain called the hypothalamus (part of the brain which controls the conditions within your body including body temperature and blood pressure).
- You have high levels of a hormone called prolactin (hyperprolactinaemia).

Also, if you are a woman do not use Menopur if:

- You have tumours of your womb (uterus), ovaries or breasts.
- You have cysts on your ovaries or enlarged ovaries that are not due to polycystic ovary syndrome (a condition that prevents eggs from being released from the ovaries).
- You have bleeding from your vagina for an unknown reason.
- You have primary ovarian failure (a condition in which the ovaries do not function properly).
- You have blocked fallopian tubes, unless you are having IVF or ICSI (intracytoplasmic sperm injection).
- You are having an early (premature) menopause.
- You have certain physical problems in your reproductive organs (womb, fallopian tubes, ovaries or cervix).
- Your womb has been removed (hysterectomy).
- You have fibroid tumours (tumours in your womb that are not cancer).
- You are pregnant or breast-feeding.

Also, if you are a man do not use Menopur if:

- You have cancer of your testicles.
- You have prostate cancer.

Do not use Menopur if any of the above applies to you. If you are not sure, talk to your doctor, nurse or pharmacist before you start using Menopur.

Take special care

Check with your doctor or nurse before using this medicine if:

- You have had infertility treatment in the past.
- You or someone in your family has had blood clots. This is because treatment with Menopur may increase the risk of having a clot. Pregnancy also increases the risk of having clots.

If any of the above applies to you (or if you are not sure), talk to your doctor, nurse or pharmacist before using Menopur.

Pregnancy and breast-feeding

If you are already pregnant or breast-feeding, you must not use Menopur.

Tests before you start treatment

Before you start treatment with Menopur, your doctor will normally do tests to check the following:

Men and women:

- Your thyroid and adrenal glands are working properly.
- You do not have tumours of the pituitary gland or hypothalamus.

Women only:

- Your ovaries are working properly.
- You do not have higher than normal blood levels of a hormone called prolactin.

Important information about some of the ingredients of Menopur

Menopur contains lactose (which is a type of sugar). If you have been told by your doctor that you cannot tolerate or digest some sugars (have an intolerance to some sugars), talk to your doctor before using this medicine.

3. How to use Menopur

Always use Menopur exactly as your doctor or nurse has told you. You should check with your doctor, nurse or pharmacist if you are not sure.

Menopur is not recommended for children or elderly people.

Using Menopur

- You will have Menopur as an injection under the skin or into a muscle.
- You will either be given Menopur by a doctor or nurse or you will be taught how to give it to yourself.
- Menopur comes as a dry powder in small bottles (vials).
- Once the dry powder has been mixed with the solvent provided, it should be used straight away.

The dose and length of your treatment

- The dose, and how long your treatment lasts, depends on why you are using Menopur and how well it works.
- Your doctor or nurse will monitor how you respond to your treatment.
- This will help them to work out what dose you need and how long you need to use Menopur for.

In women:

Infertility (to help follicles to mature):

- If you are having periods, your treatment will start within the first 7 days of your menstrual cycle.
- You may use Menopur daily for up to 3 weeks.
- Or, you may use Menopur every other day for 6 days (three doses in total).

'Assisted conception' such as IVF:

- The usual dose is 75 to 300 IU each day.
- Your doctor will decide how long you need to use Menopur for.

In men:

For low sperm count:

- The usual dose is 75 or 150 IU two or three times a week.
- Treatment is normally continued for at least 3 or 4 months.

Instructions for use:

If your doctor has asked you to inject Menopur yourself, you should follow the instructions provided on **Page 2**.

If your clinic has asked you to inject Menopur yourself, you should follow the instruction provided by them.

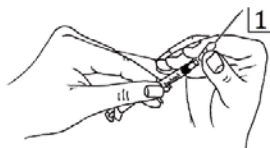
The first injection of Menopur should be given under the supervision of a doctor.

DILUTING MENOPUR:

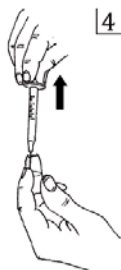
Menopur is provided as a powder and must be dissolved before it is injected. The liquid (solvent) which you should use to dilute Menopur is provided with the powder. Menopur should only be diluted immediately before use.

continued →

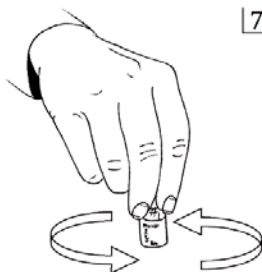
What to do:



1. Firmly attach the long, thick needle (drawing up/reconstitution needle) to the syringe.
2. Break the liquid ampoule with the dot pointing towards yourself.
3. Insert the needle in the liquid ampoule.



4. Draw up all the liquid from the ampoule into the syringe.
5. Insert the needle through the rubber top of the powder vial and slowly inject all of the liquid. Aim at the side of the vial, to avoid creating bubbles.
6. The powder should quickly dissolve (within 2 minutes) to form a clear solution.



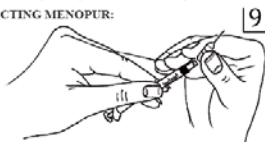
7. To help the powder dissolve, swirl the solution. Do not shake as this will cause air bubble to form.

If the solution is not clear or if it contains particles it **SHOULD NOT** be used.

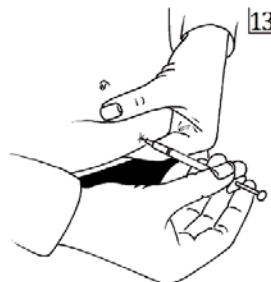
8. Draw up the solution back into the syringe.

If you have been prescribed more than one vial of Menopur powder per injection, you can draw up the solution (the first Menopur solution) back into the syringe and inject it into a second vial of powder. You can do this with up to three vials of powder in total - but only do as your doctor has told you.

INJECTING MENOPUR:



9. Once you have your prescribed dose drawn up into the syringe, change the needle to the short, thin needle (the injection needle).
10. Turn the syringe with the needle upwards and flick it gently so if any air bubbles, they are collected at the tip. Depress the plunger carefully until the first drop of fluid comes out.
11. Your doctor or nurse will tell you where to inject (e.g. front of thigh, abdomen etc.).
12. Disinfect the injection site.



13. To inject, pinch the skin to produce a fold, and insert the needle in one swift motion at 90 degrees to the body. Press down on the plunger to inject the solution, and then remove the needle.
14. After removing the syringe, apply pressure to the injection site to stop any bleeding. Gently massaging the injection site will help to disperse the solution under the skin.
15. Do not put used items into normal domestic wastes, these should be disposed of appropriately.

If you use more Menopur than you should

If you think you have used too much Menopur, tell your doctor, nurse or pharmacist.

If you forget to use Menopur

If you think you have missed a dose, tell your doctor, nurse or pharmacist.

4. Possible side effects

Like all medicines, Menopur can cause side effects, although not everybody gets them.

Side effects that can happen in women:

If you notice any of the following signs, tell your doctor straight away. It may mean that your ovaries have been stimulated too much and you may need urgent medical treatment. This side effect is common (affects less than 1 in 10 people).

- Feeling sick.
- Being sick.
- Diarrhoea.
- Pain or swelling of the tummy.
- Weight gain.
- Difficulty breathing.
- Feeling more thirsty than usual.
- Producing less urine when you go to the toilet or going to the toilet less often.

If you notice any of the above signs, tell your doctor straight away.

If treatment with Menopur results in pregnancy

The following are more likely to happen in women who have had fertility treatment than in women who have got pregnant (conceived) naturally:

- Being pregnant with more than one baby. This carries an increased risk of problems for the mother during the pregnancy and at or around the time of birth.
- The fertilised egg implanting outside the womb (ectopic pregnancy). This is more likely if you have had tubal disease in the past (a condition where the fallopian tubes are blocked or damaged).
- Miscarriage or abortion.
- A slightly higher risk of your baby being born with physical defects.

Your doctor will be able to discuss this with you before you start treatment.

Side effects that can happen in both women and men:

Common (affects less than 1 in 10 people):

- Headache.
- Feeling sick (nausea).
- Being sick (vomiting).
- Pain or swelling of the tummy (abdomen).
- Pain or inflammation where the injection was given.

Uncommon (affects less than 1 in 100 people):

- Blood clots in the veins, usually of the leg (deep vein thrombosis).

Very rare (affects less than 1 in 10,000 people):

- Allergic reactions.
- If Menopur is used for a long time, your body may make antibodies which can stop the treatment from working.

If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

5. How to store Menopur

- Keep out of the reach and sight of children.
- Do not use Menopur after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.
- Store below 25°C.
- Store in the original container to protect from light.
- Do not freeze before or after reconstitution.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information

What Menopur contains

- Menopur is a sterile freeze dried powder for injection. The active substance is Highly Purified Menotrophin. Each vial contains 150 IU of the active substance, corresponding to 150IU of FSH activity and 150IU of LH activity.
- The other ingredients for powder are Lactose monohydrate, Polysorbate 20, Sodium hydroxide and Hydrochloric acid.
- The solvent contains Sodium chloride, Hydrochloric acid and Water for injection.

What Menopur looks like and contents of the pack

Menopur is supplied in cartons of five or ten clear glass vials which contain a white to off-white powder. The carton also contains an equal number of clear glass ampoules containing a colourless solvent.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Ferring Pharmaceuticals Ltd., The Courtyard,
Waterside Drive, Langley, Berkshire, SL3 6EZ.
PL 03194/0109

Manufacturer:
Ferring GmbH, Wittland 11, D-24109 Kiel, Germany

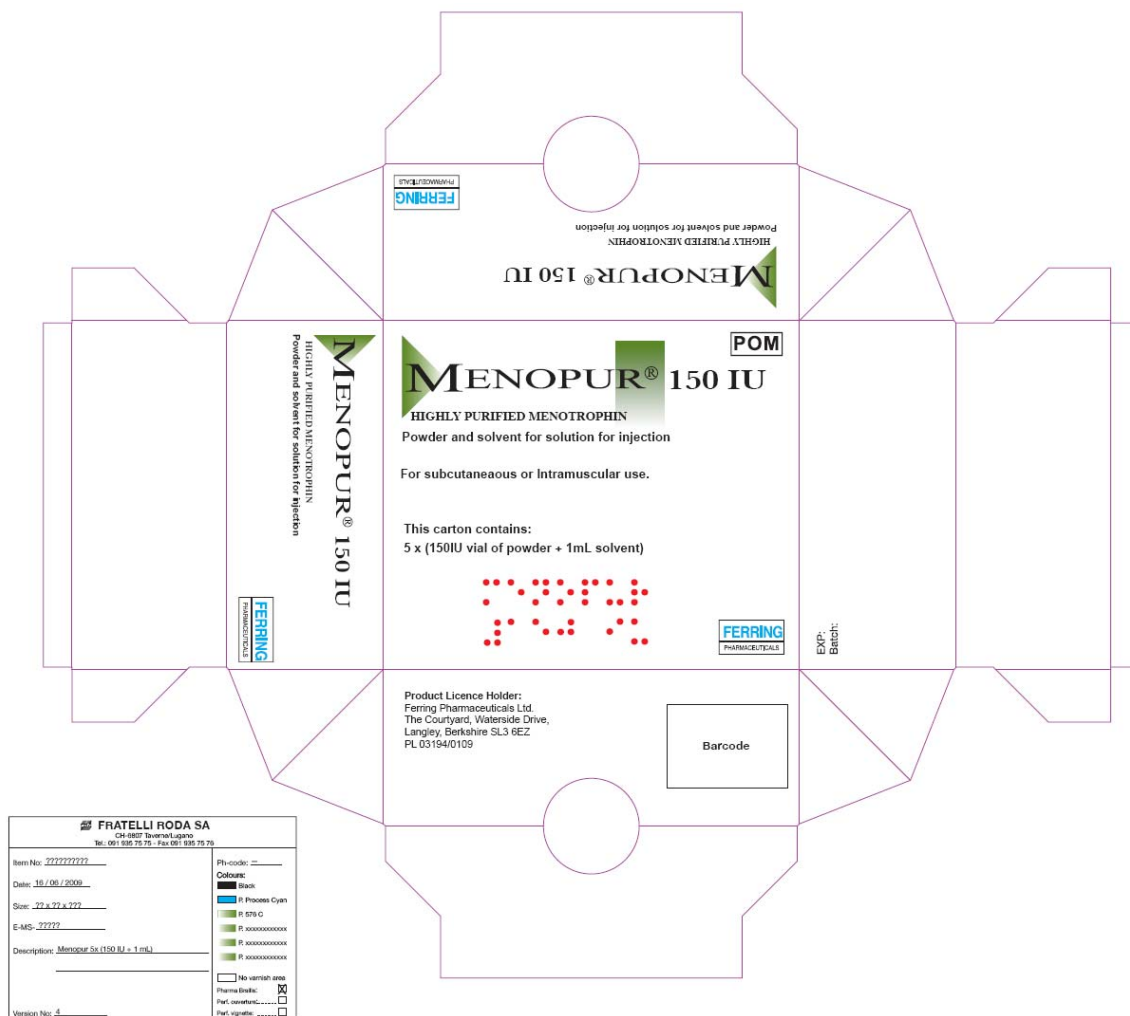
This leaflet was last revised in December 2010.

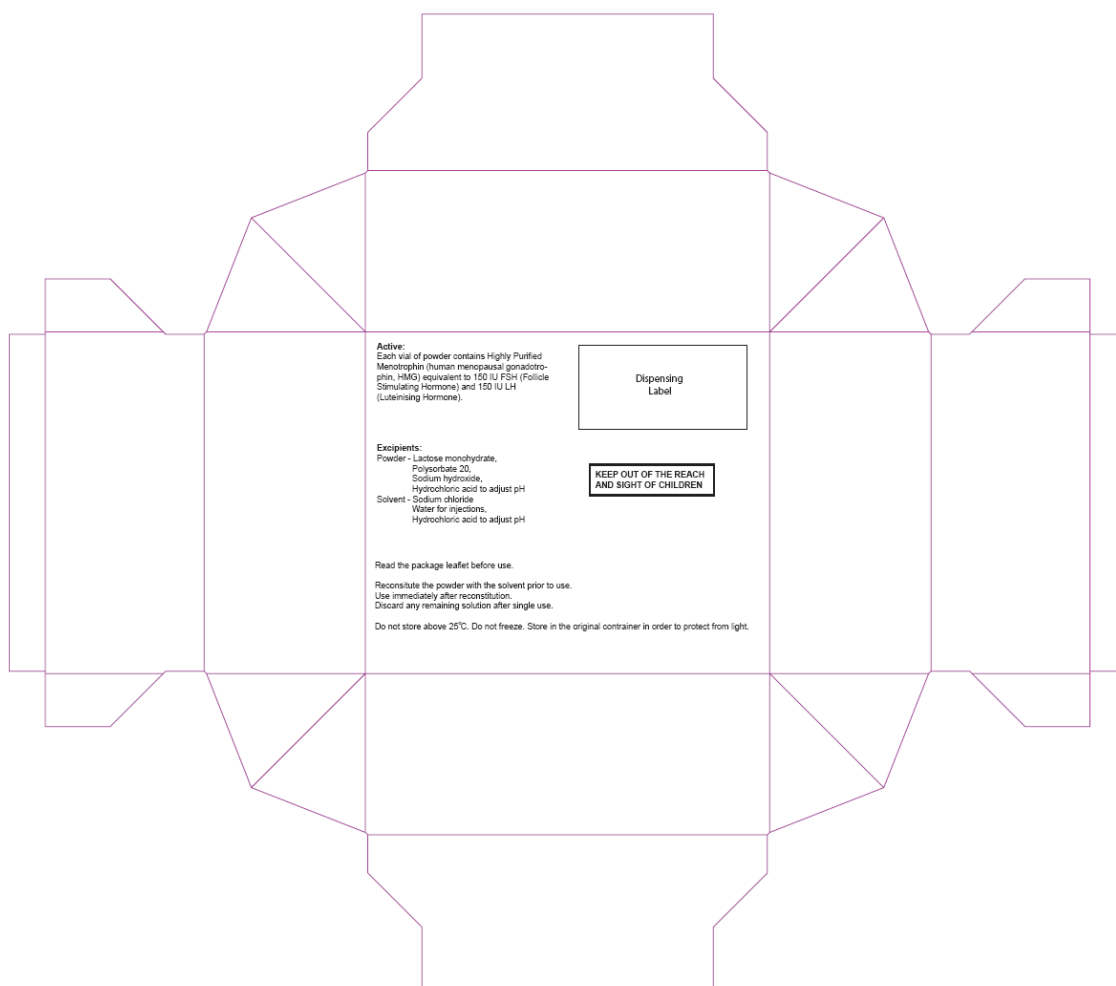
Menopur is a registered Trademark.

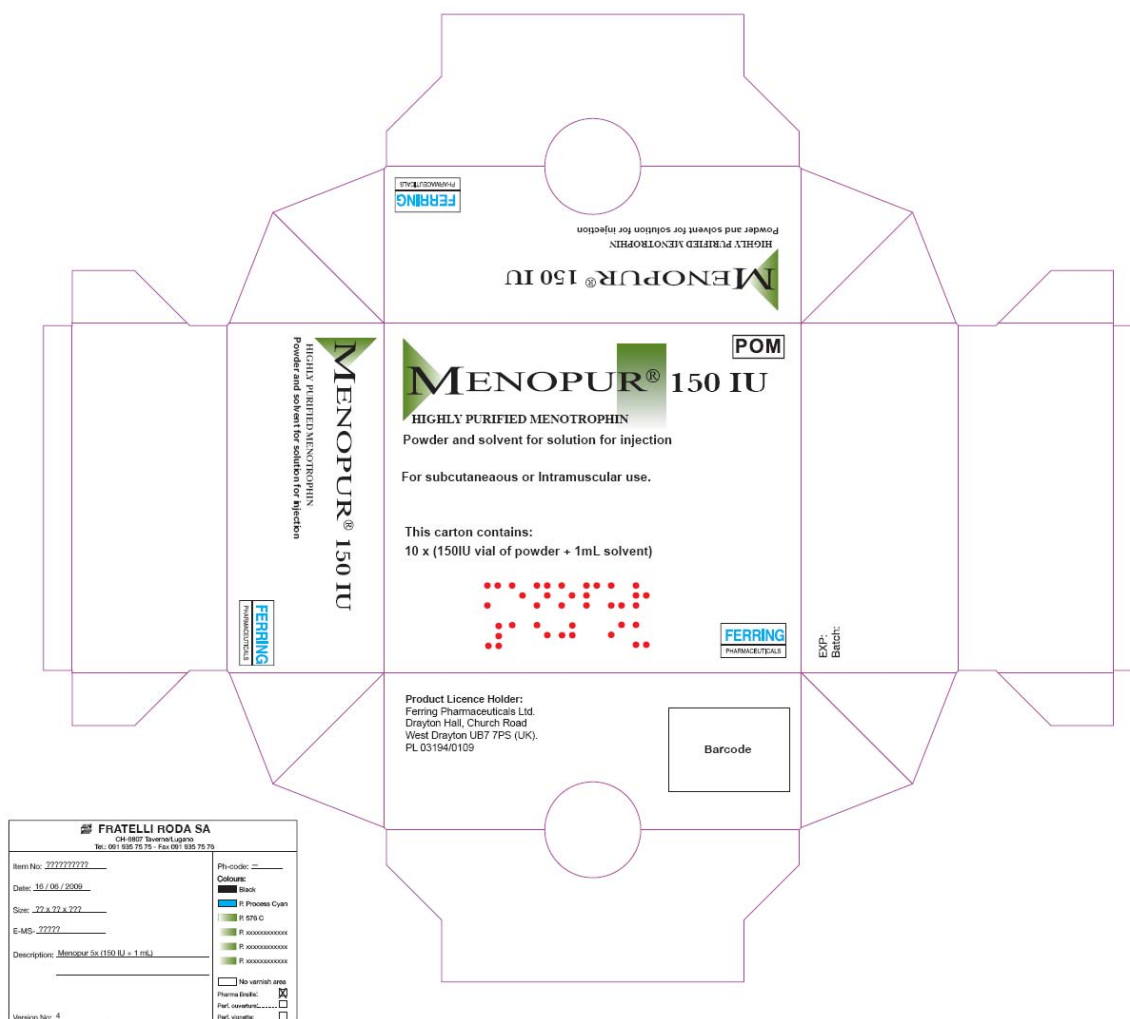


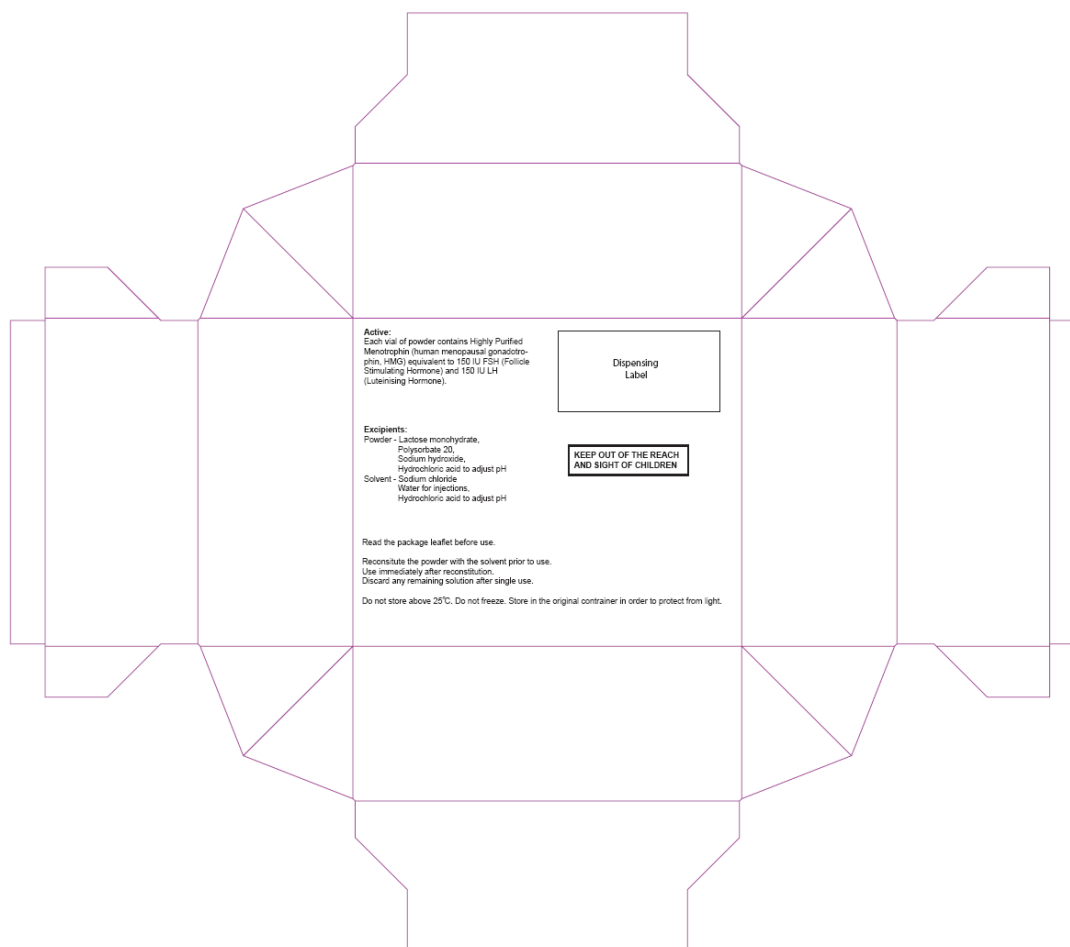
Labelling

**Menopur 150 IU
Powder and solvent for solution for injection
(menotrophin)
PL 03194/0109**









MENOPUR® 150IU**POM**

Powder for solution for injection
Menotrophin equivalent to 150IU
FSH + 150IU LH per vial.
For S.C. or I.M. use.
PL 03194/0109

FERRING
PHARMACEUTICALSBatch:
Expiry:**MENOPUR® 150IU**

Solvent for solution for
injection. 1ml of solvent.
For S.C. or I.M. use.
PL 03194/0109

POM**FERRING**
PHARMACEUTICALSBatch:
Expiry: