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IRISH MEDICINES BOARD

PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

Menopur 600 and 1200 IU Powder and Solvent for Solution for Injection

MENOTROPHIN

PA 1009/015/002 & 003

The Public Assessment Report reflects the scientific conclusion reached by the Irish Medicines Board (IMB) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the IMB for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the IMB leading to the approval of the medicinal product for marketing in Ireland.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the IMB has granted a marketing authorisation for Menopur 600 and 1200 IU Powder and Solvent for Solution for Injection, from Ferring Ireland Ltd on 17th June 2011 for treatment of anovulation, including polycystic ovarian disease (PCOD), in women who have been unresponsive to treatment with clomiphene citrate and 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).

The application to market this product is submitted in accordance with 8(3), known active substance, of Article 2001/83/EC. The application is a line extension of Menopur 75 IU powder and solvent for solution for injection (PA1009/15/01) which was first approved in Ireland on 4 May 2001, with the addition of these products as new strengths.

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the IMB's website at www.imb.ie

Name of the product	Menopur 600 and 1200 IU Powder and Solvent for Solution for Injection
Name(s) of the active substance(s) (INN)	MENOTROPHIN
Pharmacotherapeutic classification (ATC code)	G03GA02
Pharmaceutical form and strength(s)	600 & 1200 IU
Marketing Authorisation Number(s) in Ireland (PA)	PA 1009/015/002-003
Marketing Authorisation Holder	Ferring Ireland Ltd

II QUALITY ASPECTS

II.1. Introduction

This application is for Menopur 600IU and 1200 IU Powder and Solvent for Solution for Injection.

II.2 Drug substance

The active substance is highly purified menotrophin (human menopausal gonadotrophin, HMG), is approximately a 1:1 ratio of follicle stimulating hormone (FSH) and luteinizing hormone (LH). Menotrophin is an established active substance described in the British Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification have been provided.

II.3 Medicinal product

P.1 Composition

Menopur 600 IU and 1200 IU Powder and Solvent for Solution for Injection is a two component product consisting of a vial containing the active accompanied by either one or two prefilled syringes containing the solvent.

The vial contains either 600 IU or 1200 IU of the active substance Menotrophin, and is qualitatively similar to the

approved presentation Menopur 75 IU powder for solution for injection (PA 1009/15/1) except for removal the components for pH adjustment and the addition of phosphate buffers. Other excipients in this formulation are lactose monohydrate and polysorbate 20. The powder is white to off-white in colour.

The 600 IU powder is accompanied by one 1ml pre-filled syringe containing water for injections and the antimicrobial preservative metacresol. Two of the pre-filled syringes, containing this clear, colourless solvent are supplied with the 1200 IU powder vial.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/Ancillary Substances)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for parenteral preparations, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production sites have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The 600 IU product is supplied as a pack of 1 vial of powder, 1 pre-filled syringe with solvent for reconstitution, 1 needle for reconstitution, 9 alcohol pads and 9 disposable syringes for administration graduated in FSH/LH units with pre-fixed needles.

The 1200 IU product is supplied as a pack of 1 vial of powder, 2 pre-filled syringes with solvent for reconstitution, 1 needle for reconstitution, 18 alcohol pads and 18 disposable syringes for administration graduated in FSH/LH units with pre-fixed needles.

The 2ml colourless glass vials have a halobutyl rubber stopper closed with an aluminium flip-off cap. The 1ml prefilled glass syringe has a rubber tip cap and plunger rubber stopper.

Evidence has been provided that the glass vials and prefilled syringes comply with Ph. Eur. requirements, while the needles and disposable syringes carry a CE mark.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 36 months when stored between 2°C to 8°C, in a refrigerator, without freezing, in its original containers in order to protect from light.

After reconstitution, an in-use shelf-life of 28 days is assigned for storage at not more than 25°C while freezing is to be avoided.

Adventitious Agent Safety

Viral validation studies with respect to manufacturing process viral inactivation capacity were deemed in compliance with EU requirements.
Scientific data has been provided for menotrophin and for lactose monohydate with respect to compliance with the Note For Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Menopur 600 and 1200 IU Powder and Solvent for Solution for Injection.

III NON-CLINICAL ASPECTS

III.1 Introduction

A new national application for Menopur 600 IU and 1200 IU powder and solvent for solution for injection has been submitted as a line extension to the already approved reference product Menopur 75 IU powder and solution for injection (PA1009/15/1).

Menopur 600 IU and 1200 IU will be administered by subcutaneous route. These products will be reconstituted in two slightly different solvents to that previously used for the approved Menopur 75 IU product. The use of two different types of solvents for Menopur 600 IU and 1200 IU (m-cresol, 3 mg/ml and sodium chloride, 7 mg/ml or m-cresol, 3.3 mg/ml) was examined to determine the local tolerance of this product.

III.2 Toxicology

Two 28-day local tolerance tests using both solvent types were examined in albino New Zealand White rabbits by both the subcutaneous (s.c.) and intramuscular (i.t.) route. Animals received single daily injections of either 0.75 mL/450 IU of Menopur 600 or 1200 IU, solvent alone or saline as control. The doses were based on the anticipated human doses. Bluish colouration (bruising) was observed on some days at all injection sites and was considered to be injection procedure related. Minimal to slight swelling and reddening was also seen at injection sites, most frequently associated with Menopur injections. Histopathology revealed local tissue reactions for all formulations but were more pronounced at Menopur sites. There was no evidence of damage to muscle by either solvent or Menopur as measured by depletion of creatine kinase. Overall, it was concluded that the clinical administration of Menopur 600 IU and 1200 IU by s.c. or i.t. routes is unlikely to result in significant local irritation, other than that observed with the normal effects of needle administration.

III.5 Ecotoxicity/environmental risk assessment

This application amounts to a new line extension to existing marketing authorizations hence, the overall increase in exposure could impact on the environment through approval of this national line extension. Therefore the applicant has performed an environmental risk assessment (ERA) and has predicted that the product is unlikely to present an environmental risk following the prescribed use in patients given that the calculated Predicted Environmental Concentration value (0.001125 □g/L) is below that of the default value of 0.01 □g/L as described in the European Medicine Agency's ERA guideline (EMEA/CHMP/SWP/4447/00).

III.6 Discussion on the non-clinical aspects

Based on the review of the pre-clinical data, it is considered that the application for the extension for Menopur 600 IU

and 1200 IU powder and solvent for solution for injection as, based on the existing marketing authorization dossier for Menopur 75 IU powder and solution for injection (PA1009/15/1), is approvable from a non-clinical perspective.

IV CLINICAL ASPECTS

IV.1 Introduction

This procedure concerns a line extension to Menopur 75 IU for two additional strengths - Menopur 600IU and 1200IU powder and solvent for solution for injection. Menopur 75 IU was originally approved in Ireland in 2001. The marketing authorisation is granted based on article 8(3) (known active substance) of Directive2001/83/EC.

The rationale for the development of two new formulations, 600 IU and 1200 IU, both with a concentration of 600 IU/mL, is to provide products that are more convenient to use for patients requiring doses higher than 75 IU/day. The IMB has been assured that GCP standards were followed in an appropriate manner in the studies conducted.
Menopur 600 IU and 1200 IU is intended for subcutaneous injection after reconstitution with the solvent provided. Menopur is a highly purified menotrophin preparation obtained from the urine of postmenopausal women comprising follicle stimulating hormone (FSH) and luteinising hormone (LH) activity.

Menopur is indicated for the treatment of 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)

IV.2 Pharmacokinetics

The applicant provided a literature based overview of the pharmacokinetic profile of FSH and LH. Absorption of proteins of this nature requires diffusion of the drug through the extracellular matrix to the lymphatic capillary system and then into the blood stream. This explains the slow initial absorption of FSH into the vascular circulation after subcutaneous administration. The rate limiting step in the vascular absorption of FSH is the lymphatic flow rate and transportation of FSH and not the initial diffusion from the site of injection to the lymph capillaries.

Table 1 Phase 1 study Menopur 1200IU

Indication	Study ID /Region	Design	Controlled / Uncontrolled	Number of subjects and main diagnosis	Test products	Regimen (start dose and duration)
Bio-equivalence	FE999906 CS05 [5.3.1.2] Europe	Randomised cross-over	Open-label	Healthy, fertile down-regulated women	MENOPUR 75IU MENOPUR 1200 IU "former"	450 IU single dose

An open-labelled, cross-over, single-centre phase I study (CS05) investigated bioequivalence between Menopur 75 IU and (former) Menopur 1200 IU (600IU/ml) after subcutaneous administration of 450 IU to healthy female subjects. 450 IU of both formulations were administered to healthy down regulated female subjects. 50 subjects were randomised 1:1 into one of the two possible treatment sequences. The FSH and LH values were baseline corrected to get as correct a picture of the pharmacokinetic profile as possible. The two formulations showed very similar PK characteristics. It can be assumed that the FSH in Menopur does not differ in distribution, metabolism or excretion from other urinary gonadotrophin preparations, or from the distribution and plasma clearance of endogenous human FSH. The pharmacokinetic parameters of LH associated with urinary menotrophin preparations have not been possible to clearly document due to the short half-life of LH and the contribution of endogenous LH.

Table 2 Summary of Derived Baseline-Corrected FSH PK Parameters

FSH	Baseline-corrected	
PK Parameter	**MENOPUR 1200 IU**	**MENOPUR 75 IU**
t_{max} [h]	N = 50	N = 50
Mean (SD)	23.6 (13.8)	23.5 (9.0)
Range	4 – 72	8 – 48
$t_{1/2}$ [h]	N = 49	N = 48
Mean (SD)	45.18 (19.43)	47.89 (21.52)
CL/F [mL/h]	N = 49	N = 48
Mean	543 (250)	504 (239)
V_z/F [L]	N = 49	N = 48
Mean	32.2 (12.7)	30.7 (13.2)

Bioequivalence was demonstrated between Menopur 75 IU and Menopur 1200 IU based on baseline-corrected FSH concentrations. The Menopur 1200 IU Multidose has been shown to be bioequivalent to the currently marketed Menopur 75 IU. Despite the different excipient content in the 1200 IU formulation, notably the addition of m-cresol and phosphate buffer compared with the 75IU formulation the 90% point estimates for AUC and Cmax of FSH were within the bioequivalence limits 0.80-1.25. The composition of the currently approved 1200 IU multidose formulation differs from the one tested in CS05 in that the current solvent for reconstitution does not contain any sodium chloride. This reduces the osmolarity of the formulation, but the activities of FSH and LH per volume are the same.

Table 3 Bioequivalence of Menopur 1200IU 'former' versus Menopur 75IU with baseline corrected serum FSH

PK parameter	Unit	MENOPUR 1200 IU		MENOPUR 75 IU			
		N	Geometric Mean	N	Geometric Mean	Geometric Mean Ratio	90% CI
$AUC_{0\text{-}144}$	mIU•h/mL	50	764.0	50	814.4	0.9381	0.8831; 0.9964
C_{max}	mIU/mL	50	11.836	50	12.602	0.9392	0.8809; 1.0013

The bioequivalence established between the 75 IU and the "former" 1200 IU formulations can be considered to support bioequivalence between the current 600 IU and 1200 IU formulations, and the marketed 75 IU formulation.
Literature reports on the bioequivalence of various products and formulations of urinary derived FSH have demonstrated bioequivalence after subcutaneous administration as well as after intramuscular administration in spite of varying composition of the formulations. Thus, these data suggest that the small differences in the formulations do not change the pharmacokinetic properties to an extent that jeopardizes bioequivalence.

Table 4 Composition of different Menopur formulations

	EU MENOPUR 75 IU Single dose	1200 IU Multidose "Former"	1200 IU Multidose "Current"	600 IU Multidose "Current"
hMG-HP	75 IU/mL	600 IU/mL	600 IU/mL	600 IU/mL
Lactose	21mg/mL	10.5mg/mL	10.5mg/mL	21mg/mL
Polysorbate 20	0.1 mg/mL	0.0025 mg/mL	0.0025 mg/mL	0.005 mg/mL
$Na_2HPO_4 \cdot 7\ H_2O$	-----	0.134 mg/mL	0.134 mg/mL	0.268 mg/mL
phosphoric acid 85%	-----	q.s. (pH 6.7-6.8)	q.s. (pH 6.7-6.8)	q.s. (pH 6.7-6.8)
m-cresol	-----	3.0 mg/mL	3.3 mg/mL	3.3 mg/mL
NaCl	9.0 mg/mL	7.0 mg/mL	-----	-----
Water	1.0 mL	2.0 mL	2.5 mL	1.0 mL

Conclusion:
The study demonstrates bioequivalence between Menopur 75 IU and Menopur 1200 IU based on baseline-corrected FSH concentrations. The difference in excipients between the formulations has been adequately justified

IV.3 Pharmacodynamics

Follicle size and oestradiol levels are well established pharmacodynamic markers of gonadotrophin treatment.

IV.4 Clinical Efficacy

No new efficacy data was presented as part of this application

Anovulation in women unresponsive to clomiphene citrate

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 was evaluated for Menopur in 2005. A total of 184 women were exposed to trial products in the pivotal clinical study submitted to support the efficacy of Menopur in anovulatory women with WHO group II infertility and unresponsive to clomiphene citrate. The efficacy evaluation of Menopur for the proposed indication was based on 91 women. The ovulation rate observed with Menopur was 85.7% among the PP population and 83.5% among the ITT population and the lower limit of the two-sided 95% confidence interval of the difference between treatments with respect to ovulation rate was within the pre-specified non-inferiority limit of -20%. The data available in the literature on the comparison between menotrophins and FSH-only preparations suggest a similar efficacy in terms of ovulation and pregnancy rates in anovulatory patients.

Controlled ovarian hyperstimulation for ART

The efficacy of Menopur for multiple ovarian follicular developments in patients undergoing ART was previously evaluated for Menopur in 2002. A total of 727 women were exposed to trial products in the Phase III pivotal clinical study submitted to support the efficacy of Menopur. Of these, 373 women were exposed to Menopur and 354 to the reference product (recombinant follitropin alfa, GonalL-F, Serono). For the PP-population with one IVF/ICSI cycle, the ongoing pregnancy rate was 24.7% in the Menopur group and 22.4% in the Gonal-F group, and 24.2% and 21.8% for the ITT-population, well within the -10% non-inferiority limit established. These results were confirmed in the MERIT study published in 2006.

IV.5 Clinical Safety

The adverse event profile in phase I study (CS05) did not reveal any differences between the two formulations of Menopur used. Headache and hot flush, recorded by approximately 35% and 20% of the subjects, respectively, were regarded to be related to the treatment in 20% and 5% of the subjects, respectively.

Post marketing experience

Menopur was first approved in Denmark on 18 November 1999. The cumulative exposure to Menopur from 18 November 1999 to 31 December 2007 is estimated at 863,084 treatment cycles, corresponding to 345,234 patients. As of 31 August 2008, Ferring Global Pharmacovigilance has registered 253 cases of adverse events following treatment with Menopur. A total of 156 cases have been assessed as related to Menopur from first launch in November 1999 to 31 August 2008. In addition to the listed events, 36 cases of ineffective treatment were reported.

Ovarian hyperstimulation syndrome (OHSS)
The most frequent serious adverse event reported was OHSS accounting for 40 reported cases. A total of four cases of OHSS associated with thromboembolic events have been reported following treatment with Menopur. The current labelling for gonadotrophins provides information on the risk of thromboembolic complications. Adherence to the recommended dosage regimen can minimise risk of OHSS and its severe forms.

Anaphylactic reactions
One case of anaphylactic reaction and one case of anaphylactic shock following treatment with Menopur have been reported. Anaphylactic reaction has been added to the labelling for Menopur to section 4.8

Conclusion
No new safety issues were identified after single dose treatment with Menopur 75 IU and Menopur 1200 IU. The preparations were well-tolerated locally.

Product information

The proposed Summary of product characteristics (SPC) and patient information leaflet (PIL) are acceptable. The PIL has undergone user testing.
Bridging data comparing each section of the leaflets for Menopur 600 IU and Menopur 1200 IU with Bravelle 75IU (UK/H/0697/001) has been provided. In addition to the bridging statements a focus test on the reconstitution procedure for Menopur 1200 IU has been successfully completed.

Risk Management Plan

Limitations of the Human Safety Database

Exposure

Total of 50 patients have been exposed to Menopur 1200 IU during the clinical study program. Concerning single dose formulation, Menopur 75 IU, 878 patients were involved in major clinical studies. During the marketed period approximately 400,000 patients have been exposed to Menopur 75 IU.

Populations not studied in the pre-approval phase.

Menopur 600IU and 1200IU are only indicated for use in women of childbearing age. No studies have been conducted in the elderly, in males or in children. Patients with clinically significant systemic disease, endocrine or metabolic abnormalities, Polycystic ovarian syndrome, who were pregnant or in whom pregnancy was contraindicated, or who had tumours of the ovary, breast, uterus, adrenal gland, pituitary or hypothalamus were excluded from clinical trials.

Identified and potential risks

Important identified risk

OHSS is the most frequent iatrogenic complication of controlled ovarian hyperstimulation and is a class effect for all gonadotrophins. The incidence of OHSS for ART has been estimated to be up to 20%, but varies between studies. A recently published literature data suggests that the incidence of OHSS in non-selected population during controlled ovarian hyperstimulation for ART is about 12%, with the incidence of severe cases being about 4%. Summary of the Product Characteristics for Menopur 600 IU and 1200 IU includes comprehensive information on the risk of OHSS,

both as special warnings and special precautions for use, and as undesirable effects. It is not expected that the risk of OHSS will be higher with Menopur 600 IU and 1200IU than with Menopur 75 IU.

Important potential risks

Menopur is a polypeptide compound, capable of causing allergic reactions. Serious allergic reactions, including anaphylactic reaction, have not been reported in clinical study program either with Menopur 75 IU, or with Menopur 1200 IU. During the post marketing period, total of two cases of anaphylactic reactions have been reported following administration of Menopur 75 IU. The risk of anaphylactic reaction has been reflected in the labelling.

Identified and Potential Interactions
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.

Potential for Off-label Use
Menopur 600 IU and 1200 IU are indicated for controlled ovarian hyperstimulation and treatment of anovulation. The risk of off-label use is low.

Summary of Safety Concern and Planned Pharmacovigilance Actions
Safety Concern and Planned Pharmacovigilance Actions

The main safety concerns are the identified risk of OHSS and the potential risk of hypersensitivity reactions. Experience in patients with hepatic or renal impairment is listed as important missing information. Extensive clinical and postmarketing experience with Menopur has not identified a safety concern in patients with impaired hepatic and renal function.

Pharmacovigilance Plan
Routine Pharmacovigilance is planned for all identified and potential risks.

Safety concern	Planned action(s)
OHSS	Routine pharmacovigilance activities
Anaphylactic reaction	Routine pharmacovigilance activities
Missing data: Experience in patients with impaired hepatic or renal function	Information are included in the labelling section 5.3 of the proposed SPC [1.3.1]

Additional Risk minimisation measures
No additional risk minimisation measures have been proposed by the applicant.
The risk of reconstitution /administration errors is a potential concern. The applicant conducted a focused user test for the PIL for the 1200IU strength which was positively concluded. The applicant has committed to reviewing this issue in subsequent PSURs.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

V OVERALL CONCLUSIONS

BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The rationale for developing the new multidose formulation is to facilitate a wider range of doses in a smaller injection volume than is currently possible with the marketed 75IU formulation. Menopur 600IU and 1200IU are line extensions of the already approved 75IU consequently no new clinical efficacy data has been submitted. Bioequivalence between the 75IU and the 600IU and 1200IU strengths was demonstrated. The difference in excipients between the formulations was adequately justified. The safety profile of Menopur is well described. No new safety concerns were identified. The SPC and PIL are acceptable. The potential for reconstitution errors with the 1200IU dose will be monitored in subsequent PSURs. The overall benefit/risk balance is considered to be positive.

The IMB, on the basis of the data submitted, considered that Menopur 600IU and 1200 IU demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.