



Australian Government

Department of Health and Ageing  
Therapeutic Goods Administration

# Australian Public Assessment Report for Gonadotrophin – human menopausal

Proprietary Product Name: Menopur

Sponsor: Ferring Pharmaceuticals Pty Limited

**October 2011**

**TGA** Health Safety  
Regulation

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- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
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- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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## I. Introduction to Product Submission

### Submission Details

<i>Type of Submission</i>	New Chemical Entity
<i>Decision:</i>	Approved
<i>Date of Initial Decision:</i>	28 February 2011
<i>Date of Final Decision:</i>	25 July 2011
<i>Active ingredient(s):</i>	Gonadotrophin - human menopausal
<i>Product Name(s):</i>	Menopur
<i>Sponsor's Name and Address:</i>	Ferring Pharmaceuticals Pty Limited PO Box 135 Pymble NSW 2073
<i>Dose form(s):</i>	Powder and solvent for solution for injection
<i>Strength(s):</i>	600 International units (IU) and 1200 IU
<i>Container(s):</i>	Colourless 2 mL glass vials, glass type I with rubber closures used in combination with an aluminium seal and a plastic cap.
<i>Pack size(s):</i>	600 IU: 1 vial powder, 1 prefilled syringe (PFS) with solvent (1 mL) plus needle 1200 IU: 1 vial powder, 2 PFS with solvent (1 mL) plus needle
<i>Approved Therapeutic use:</i>	Anovulatory infertility, 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 intrafallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI).
<i>Route(s) of administration:</i>	Subcutaneous
<i>Dosage:</i>	Infertility: Maximum daily dose 225 IU. Ovarian hyperstimulation: Maximum daily dose 450 IU.
<i>ARTG Number (s):</i>	161984, 161985

### Product Background

This AusPAR describes the evaluation of a submission by Ferring Pharmaceuticals Pty Limited (the sponsor) to register Menopur containing human menopausal gonadotrophin (HMG). A previous application for Menopur 75 International Units (IU) was withdrawn in 2004 due to chemistry and quality control issues. The sponsor stated in its letter of application that questions raised in that submission and recommendations relating to nonclinical and clinical evaluations had been addressed in the current submission. This application was submitted as a new chemical entity and the sponsor confirmed that in this

instance it is a “stand-alone application supported by extensive toxicological and clinical studies.”

The sponsor stated in its letter of application that menotrophin preparations have “different pharmacodynamic effects” compared to preparations with follicle stimulating hormone (FSH) activity alone. The two submitted studies in women undergoing controlled ovarian stimulation (COS) showed noninferiority to recombinant (r) FSH in terms of ongoing pregnancy rates (after one treatment cycle). The sponsor also stated that “a prospectively designed integrated analyses of these two studies by fertilisation method showed that Menopur resulted in statistically significantly higher clinical and ongoing pregnancy rates than Gonal-f (follitropin alfa) in in vitro fertilisation (IVF) cycles”.

The sponsor noted that another rationale for registration of this product is that it provides a wider choice for individualised treatment for a patient.

Pergoveris (follitropin alfa and lutropin alfa), Gonal-f (follitropin alfa), Puregon (follitropin beta) and Ovidrel (choriogonadotropin alfa) are some of the recombinant products that are on the Australian Register of Therapeutic Goods (ARTG) for ovulation induction, to stimulate follicular development and to trigger ovulation.

The starting raw material is urine collected from menopausal and postmenopausal women in Buenos Aires, Argentina. The urine is collected from voluntary donors on a regular basis. This raw material is subject to purification processes and is also subject to viral inactivation and viral removal studies prior to yielding the final “to market” formulation.

The application describes the presentation of Menopur in the following three formulations, all designed for either intramuscular (IM) or subcutaneous (SC) injection:

Menopur 75 IU: This product is designed for single administration of doses of 75 IU or multiples thereof. (This part of the submission was withdrawn during the evaluation process.)

Menopur 600 IU: This product is designed for the administration of multiple variable doses; the powder is presented in a glass, rubber capped vial and the 1 mL solvent is contained in a prefilled syringe.

Menopur 1200 IU: This product is similar to Menopur 600 IU except that the powder in the rubber capped vial contains 1200 IU HMG although the quantities of excipients are identical to those for the 600 IU formulation.

The proposed indications were as follows:

*Anovulatory infertility, including 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).*

*In males, insufficient spermatogenesis caused by hypogonadotropic hypogonadism.*

This part of the submission (male indication) was withdrawn during the evaluation process. In addition, the IM route of administration was withdrawn during evaluation.

These are essentially the same as the proposed indications referred to in the 2004 clinical evaluation of the original application except that the language has been modernised, polycystic ovarian disease (PCOD) is specifically mentioned, and ICSI is specifically mentioned among the ART procedures.

## Regulatory Status

Menopur has been approved for use in females in over 90 countries of wide geographical distribution; the United Kingdom, USA, Canada, countries in continental Europe including Eastern Europe, Africa, the Middle East, South Central America and the Caribbean, and in Asia or India. It is under evaluation in New Zealand where an application was submitted in August 2006. The approval dates cover the period early 1999 (UK and several European countries) to 2010 when approval has been given in a variety of regions. The indications are variously described as infertility female, IVF, ovulation induction or ART but appear similar to those submitted in Australia.

Male use has been less widely approved and is listed for 38 countries of no particularly different geographical distribution. It is approved in the UK and in most but not all of the European countries, for example not in Croatia, Denmark, Finland, Germany, Greece, Italy, Norway, Sweden, Switzerland, Turkey or the Ukraine, and specifically not in Canada or the USA. The application does not mention the basis for these differences.

## Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

## II. Quality Findings

### Drug Substance (active ingredient)

#### Structure

Luteinising Hormone (LH), human Chorionic Gonadotropin (hCG), and Follicle Stimulating Hormone (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.

#### Manufacture, Physical and Chemical Properties

There have no changes since the original submission.

#### Specifications

The specifications were reviewed and found to be satisfactory.

#### Stability

It was recommended that the drug substance be retested after 36 months at 2-8°C.

#### Characterisation

The product is human menotrophin (a 1:1 ratio of FSH and LH activity) purified from the urine of postmenopausal women. A previous application for registration was withdrawn because of inadequacies in the submission

During that evaluation, the characterisation was assessed and the glycosylation profile was found inadequate in the following respects:

While allowances were made for the complexity of Menopur (mixture of FSH/LH), the following is the minimum acceptable standard of data for glycosylation profile that needs to be provided:

1. Characterisation: oligosaccharide profiling of the purified active ingredient, final product and of purified FSH with identification of the major peaks.

2. Batch analysis: oligosaccharide profiling of no less than three batches giving numerical proportions of the major peaks.
3. Active ingredient and/or final product specifications: an assay developed and validated which will give clear indication of the glycosylation profile - this may be a comparative assay (conforms to standard profile) or a quantitative one.

The sponsor sought to address these issues in the current submission and several questions were raised:

1. As observed in the original submission, the charge status of Menopur is anomalous compared to published quantitations for pituitary derived human gonadotropins, having significantly lower proportion of non- and mono-charged glycans and greater di- and tri-charged glycans. The sponsor was requested to provide any data or publications to indicate that this anomalous glycosylation is found in other urine derived gonadotrophins. No data were provided.
2. No indication of the level of sulphation was given. The sponsor was requested to provide data to indicate this level. The sponsor did not have any data on the level of sulphation but supposed on the basis of published data that it would be low.
3. The sponsor suggested that the drug substance may be tested periodically in comparison to the reference standard using enzymatic (PNGase-F) cleavage and HPAEC-PAD to profile the glycans in the glycoprotein mixture. This suggestion was considered to be a satisfactory compromise but it was requested that the sponsor clarify what is meant by "periodic."

In response the sponsor agreed to characterise the glycosylation profile by HPAEC-PAD against the reference standard "not less than once a year as routine process validation". The test would also be included in any process validation of a significant change to the manufacturing process.

The evaluator indicated that this was not satisfactory. Even if the process is stable and consistent, checking the glycosylation only annually would potentially allow too many deficient batches onto the market before being detected.

Speculation on the clinical effect of the observed anomalous glycosylation was not possible except to emphasise that:

1. The definition of human menotrophin in the British Pharmacopoeia (BP) is: "Menotrophin is a dry preparation containing glycoprotein gonadotrophins possessing follicle-stimulating and luteinising activities. It contains not less than 40 IU of follicle stimulating hormone activity per mg. The ratio of IU of luteinising hormone (LH) activity to IU of follicle stimulating hormone (FSH) activity is approximately 1. The preparation is exclusively or predominantly of pituitary origin and obtained from the urine of postmenopausal women but, where necessary, chorionic gonadotrophin obtained from the urine of pregnant women may be added to achieve the above ratio." The activity of LH in Menopur is claimed to be verging on zero and the luteinising activity is almost solely due to hCG. This means this product does not conform to the monograph and cannot be termed "human menotrophin."
2. hCG has a much longer circulatory half-life than LH. So while it may have similar luteinising activity the pharmacokinetics are likely to be significantly different. Humegon had substantial levels of LH which were boosted by added hCG, whereas the manufacturer of Menopur claims to have very little LH. Given this precedent, the evaluator recommended rejection of this application.

3. The sponsor tacitly agreed that the product would have an inflated potency which would be exacerbated by the longer half-life of hCG.

In addition the sponsor appeared unwilling to ensure the quality of the glycosylation in any ongoing regular fashion. As such, on quality control grounds it is not of a comparable standard to those products for the same indication already registered in Australia.

The sponsor noted that this section is incomplete as it neither summarises nor alludes to a number of documents, particularly the sponsor's response to the second round glycosylation report, the "revised" second round glycosylation report dated 7 July 2010 and the resolution of Pharmaceutical Subcommittee (PSC) of the Advisory Committee of Prescription Medicines which resolved that "in particular, significant deficiencies were identified in the data submitted in relation to glycosylation/characterisation of the products. The PSC differed from the evaluator in the interpretation of the relevant BP monograph, but agreed that the gonadotropins were anomalously glycosylated."

## Drug Product

### Formulation

The formulation is shown in Table 1.

**Table 1: Menopur formulations**

Component	Amount per vial		Quality standard <sup>1</sup>
	600	1200	
Menotrophin HP	600 IU FSH 600 IU LH	1200 IU FSH 1200 IU LH	BP /Ferring
Lactose monohydrate	21 mg	21 mg	Ph.Eur./USP
Polysorbate 20	0.005 mg	0.005 mg	Ph.Eur./USP
Sodium hydroxide	-	-	Ph.Eur.
Hydrochloric acid	-	-	Ph.Eur.
Sodium phosphate dibasic heptahydrate	0.268 mg	0.268 mg	USP
Phosphoric acid 85% as a 1 M solution	qs	qs	Ph.Eur./USP
Sodium phosphate dibasic heptahydrate as a 0.5 M solution	qs	qs	USP

### Manufacture

The manufacturing process is a standard aseptic filling and lyophilisation procedure. The process comprises compounding and filtration of the solution, filling of the solution into vials with semi-closing, lyophilisation, closing of vial and capping.

The product is sterilised by means of filtration through two sterilising filters. Integrity of the sterile filters was proven prior to filtration.

<sup>1</sup> BP: British Pharmacopoeia, Ph. Eur.: European Pharmacopoeia, USP: United States Pharmacopoeia



## Specifications

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product were reviewed and were found to be satisfactory. Appropriate validation data were submitted in support of the test procedures.

## Stability

Based on the results obtained in the stability studies, the following shelf life and storage conditions were considered justified for the drug product:

Menopur powder for solution for injection (600 IU/1200 IU) is stable for 36 months refrigerated at 2-8°C.

Menopur 600/1200 IU solution for injection is stable for 28 days at room temperature (20-25°C).

## Biopharmaceutics

A randomised, controlled, open labelled, two period, two treatment crossover Phase I single dose study was conducted to investigate the bioequivalence of Menopur 75 IU and Menopur 1200 U after subcutaneous administration of 450 IU to 50 healthy female subjects.

The geometric mean ratios and 90% confidence intervals resulting from the study are shown in Table 2.

**Table 2: Pharmacokinetic (PK) parameters for Menopur**

PK parameter	Unit	MENOPUR 1200 IU		MENOPUR 75 IU		Geometric Mean Ratio	90% CI
		N	Geometric Mean	N	Geometric Mean		
AUC <sub>0-144</sub>	mIU•h/mL	50	764.0	50	814.4	0.9381	0.8831; 0.9964
C <sub>max</sub>	mIU/mL	50	11.836	50	12.602	0.9392	0.8809; 1.0013

The results suggest Menopur 1200 IU and Menopur 75 IU are bioequivalent with respect to both the area under the serum concentration time curve (AUC) and the maximal serum concentration (C<sub>max</sub>).

It was noted that the Menopur 1200 IU formulation was not the “current” formulation. The composition of the “current” 1200 IU formulation does not contain sodium chloride which is in the “former” 1200 IU formulation and thus the “current” product has a lower osmolarity. The sponsor provided a justification that the “current” 1200 IU formulation and the 75 IU formulation are likely to be bioequivalent. This justification was referred to the Delegate for consideration and deemed to be acceptable. The sponsor also provided an acceptable justification for not providing bioequivalence data on the 600 IU product.

## Quality Summary and Conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological and biopharmaceutic data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA. The sponsor withdrew the application for the 75 IU strength during the evaluation.

The evaluator considered that the application for the registration of Menopur (human menotrophin) powder for injection 600 and 1200 IU should be rejected on the grounds that the product does not conform to the monograph leading to possible extended luteinising activity and is anomalously glycosylated possibly leading to inflated potency.

### **III. Nonclinical Findings**

#### **Introduction**

There were three dose presentations (75 IU, 600 IU and 1200 IU), each with a slightly different formulation (although the application for the 75 IU presentation was withdrawn during the evaluation). Menopur is intended for SC or IM administration with a maximum daily dose of 450 IU. The previous submission for Menopur, which was for the 75 IU formulation only, was withdrawn by the sponsor due to unresolved quality issues. However, a number of deficiencies were also identified in the nonclinical evaluation report. These included the absence of repeat dose toxicity studies, allergenicity studies and studies to assess local tolerance following repeated injection. The current submission addressed these deficiencies with new data in the form of a repeat dose toxicity study, local tolerance studies and an expert statement justifying the absence of an allergenicity study provided.

#### **Toxicology**

##### **Repeat dose toxicity**

One repeat dose study of 4 weeks duration in rats was submitted. This Good Laboratory Practice (GLP) compliant study was adequately conducted and the duration of dosing of acceptable length, given the extensive clinical use of this product. The maximum recommended clinical dose is 450 IU/day or 9 IU/kg/day for a 50 kg individual. AUC data were not determined, but plasma FSH levels measured 2 hours after dosing indicated the animals were adequately exposed except for high dose animals where data indicated the production of neutralising antibodies by the end of the study. Menopur was administered via one of the clinical routes (SC) and the doses used in the toxicity study ranged from 6–60 IU/kg/day ( $\leq 6.7$ -fold the maximum recommended clinical dose on an IU/kg basis). Gonal-f, which contains recombinant FSH, was used as a comparator in the study. Pharmacological activity was evident with higher levels of testosterone in Menopur treated males compared with control males. However, there was no apparent effect on oestradiol levels in any of the treatment groups.

Toxicity findings were primarily in the reproductive system, consistent with the pharmacological activity of FSH and LH and subsequent hormonal perturbations. These included: pituitary enlargement (in females), a reduction in thymic weight with associated atrophy (males and females), increased adrenal weights (females), ovarian stimulation with increased weight and follicular cysts, vaginal mucification, uterine epithelial hypertrophy, increased secretory activity, acinar proliferation and acinar epithelial hyperplasia of mammary tissue (females) and epithelial hyperplasia in the seminal vesicles (males). These effects, in general, occurred at doses  $\geq 20$  IU/kg/day or greater than twofold the maximum recommended clinical dose. There were no unanticipated toxicities.

Antibody production to LH or FSH was not examined in this study. However, lower serum levels of human FSH were observed on Day 29 than on Day 1 in rats treated with 60 IU/kg Menopur, suggesting these animals had produced neutralising antibodies to this component. Gonal-f treated animals did not show a reduction in FSH levels, suggesting the two forms of FSH are antigenically distinct.

Although repeat dose toxicity was only examined following SC administration, this was considered acceptable as systemic toxicity would be expected to be similar for the two routes of administration and local toxicity was examined in separate specialised studies.

### **Local tolerance**

Two submitted studies monitored local reactions following multiple IM or SC injections of the 600 IU or 1200 IU formulations of Menopur in rabbits. The dose tested was the maximum recommended clinical dose of 450 IU/day. Similar observations were made in both studies with no obvious treatment related reactions or muscle damage following IM injection. SC injection sites displayed marginally greater inflammation following treatment with Menopur compared with the control solution. Overall, treatment via IM or SC injection appeared to be well tolerated.

Studies assessing local reactions following a single IM or SC injection of the 75 IU formulation were submitted in the previous application. As with the other two formulations, local reactions were unremarkable.

### **Allergenicity**

The sponsor provided a justification for the absence of allergenicity studies, claiming animal anaphylaxis tests can have poor predictive value for reactions in humans and cited the TGA-adopted European Union (EU) guidance and published papers.<sup>2,3,4</sup> Given the arguments put forward by the sponsor and the extensive clinical use of Menopur, the absence of allergenicity studies was considered acceptable. However, based on the presumptive production of FSH neutralising antibodies in Menopur treated rats and not Gonaf treated rats, a difference in the antigenicity profile of the FSH component clearly exists between these two products.

### **Nonclinical Summary and Conclusions**

Data submitted addressed deficiencies identified in the previous nonclinical report and included a repeat dose toxicity study, local tolerance studies and an expert statement justifying the absence of an allergenicity study.

The submitted repeat dose toxicity study was of 4 weeks duration and conducted in rats using SC doses up to ~7-fold the clinical dose. Toxicity findings were primarily in the reproductive system, consistent with the pharmacological activity of FSH and LH and subsequent hormonal perturbations. There were no unanticipated toxicities.

Two submitted studies monitored local reactions in rabbits following multiple IM or SC injections of the 600 IU or 1200 IU formulation. Treatment via IM or SC injection appeared to be well tolerated with no apparent reaction or muscle damage following IM injection and only marginally greater inflammation than control solutions following SC injection.

The absence of allergenicity studies was considered acceptable.

There were no objections on nonclinical grounds to the registration of Menopur.

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<sup>2</sup> EMEA, Committee for Proprietary Medicinal Products (CPMP), 16 July 1997. ICH Topic S6. Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, CPMP/ICH/302/95.

<sup>3</sup> Weaver et al. Detection of systemic hypersensitivity to drugs using standard guinea pig assays. *Toxicology* 2003; 193:203–217.

<sup>4</sup> Weaver et al. Evaluation of a lymph node proliferation assay for its ability to detect pharmaceuticals with potential to cause immune-mediated drug reactions. *J Immunotox* 2005; 2: 11–20.

## IV. Clinical Findings

### Introduction

The submission contained full reports of the following clinical studies.

- Study CS05: a bioequivalence study which compares the 75 IU with the 1200 IU formulation;
- Study 2002-03: a bioavailability study of the then proposed US Menopur with the EU Menopur;
- Study 2000-03 which for the purpose of this application provides information on the comparator pharmacokinetics of subcutaneous (SC) and intramuscular (IM) administration of the product.

There were two efficacy studies:

CS 003 (pivotal to the application) and CS 002 which support the use of the product for controlled ovarian hyperstimulation (COH) and anovulatory infertility (OI) respectively, accompanied by additional data in the form of an integrated analysis of randomised clinical trial (RCT) data on COH for ART. The included studies provide data on 1055 female subjects who received the study medication, of who 594 received Menopur.

### Pharmacokinetics

#### Study CS05

**Study CS05** was a bioequivalence study that compares the 75 IU with the 1200 IU formulation. Details of this study are briefly described in Section II. It was conducted in Germany between July 2006 and March 2007. This single centre study is of some importance, as the 75 IU single dose and the higher strength multidose formulations differ considerably in drug concentration and injection volume and it is necessary to ensure that there is a consistency of pharmacokinetic response between the two. Only a single dose level (450 IU) was studied but it is in the mid range of the upwardly titrated doses likely to be used and appears a reasonable choice.

Healthy women, taking the oral contraceptive and aged between 20 and 39 years, were recruited. Mean body weight was 64 (range 48-84) kg. For each subject, the study lasted approximately 3 months; following pre-trial assessments, there was a one month run-in period when the oral contraceptive was ceased (Day minus 28) and the GnRH agonist triptorelin acetate (Decapeptyl), 3.75 mg in 1 mL, was given intramuscularly on Days minus 28 and minus 7 so as to achieve down regulation of gonadotrophin secretion and minimise interference by endogenous hormone secretion with measurement of FSH, LH and hCG arising from the administered drug supplements.

Each subject was then given one 450 IU dose of each of the two strengths of Menopur, the subcutaneous injections being given on the mornings of Days 0 and 14, with either the 75 or 1200 IU strength given first according to a computer generated random number sequence.

Prior to administration of each dose of Menopur, pituitary down regulation was ensured by establishing that plasma oestradiol was <50 pg/mL on Days minus 3 and minus 1. The protocol specified that data from insufficiently down regulated patients was not to be used but this provision did not have to be implemented.

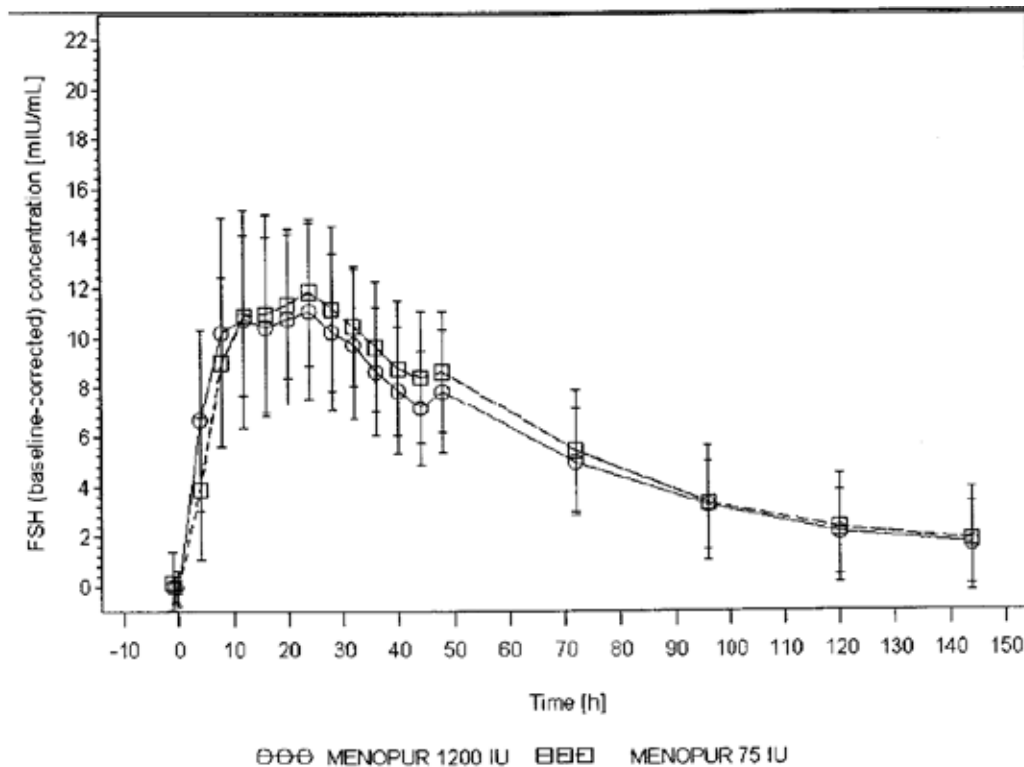
There were no major protocol deviations and all enrolled patients completed the study.

The results for the specified primary outcome parameters: AUC for time zero to 144 hours ( $AUC_{0-144}$ ) and  $C_{max}$  for baseline corrected FSH, are shown in Table 2 (Section II).

The investigators also included a statistical analysis of the uncorrected FSH data, both by ANOVA (analysis of variance) and ANCOVA (analysis of covariance).

In all of these analyses, the two formulations readily meet the established criteria for bioequivalence with the 90% confidence interval (CI) being within the bounds 0.80-1.25. Nevertheless, failure of the 90% CI for AUC to cross unity in any of the analyses, and for  $C_{max}$  only marginally so, raises the possibility of a minor but significant difference in drug exposure of approximately 5% between the two strengths (75 IU > 1200 IU). Such a difference would not be important in clinical practice. The similarity of the pharmacokinetic profiles of the two formulations is illustrated in Figure 1.

**Figure 1: Pharmacokinetic profile for the two Menopur formulations**



The FSH levels in Figure 1 are displayed as mean $\pm$ SD (standard deviation). The potential difference in mean response between the two products would be insignificant compared with the wide variance in response. It is not clear whether this is truly a between subject variability and simply random variation between doses, as within subject data, with each woman acting as her own control, is not presented.

Other derived pharmacokinetic parameters for FSH were similar for the two formulations. Terminal half life was 35 hours and 37 hours following the 75 IU and 1200 IU preparations respectively. For plasma clearance, the corresponding values were 464 and 503 mL/h and for volume of distribution, 28 and 30 L.

Serum LH, as measured by immunoassay, shows no discernible increase from baseline values. Serum hCG was below the assay limit of detection at baseline in all subjects, consistent with their non pregnant premenopausal state and rose following administration of Menopur in a time profile similar to that of FSH. Again, slightly higher mean values, but with wide variance, were noted following the 75 IU preparation and the

relationship between the two preparations both qualitatively and quantitatively appears similar to that as assessed by FSH measurement.

The only adverse event (AE) occurring with significant frequency was headache, reported by 36% of subjects overall. This was felt to be treatment related in 18% and 22% of the Menopur 75 and 1200 IU groups respectively. There was also a significant pattern of headache reported in following the GnRH agonist therapy, as is known to occur with that class of drug.

In summary, the criteria for bioequivalence between the 75 IU and 1200 IU preparations were met although the data suggest the possibility of slightly less bioavailability from the 1200 IU preparation than the 75 IU preparation, at least under the conditions of administration in this study with regard to the amounts of diluent and injection concentrations and volumes.

### **Study 2003-02**

**Study 2003-02** was a multicentre, open label, randomised, single dose, two period crossover study to compare a proposed (in 2002) US commercial formulation with the existing registered European formulation of Menopur. The US formulation of Menopur is also known by the tradename *purified Repronex* and is referred to by this name in several parts of the application. It was conducted at three USA sites from June 2003 to November 2003. Study participants included 57 healthy females, aged 18-40 (mean 28) years, body mass index (BMI) 19.7-29.2 (mean 24.0) given 400 IU doses of each preparation in random order, following down regulation of FSH secretion with leuprolide, 2 x 3.75 mg for the first treatment period and 1 x 3.75 mg before the second.

The formulations compared were each in the 75 IU single dose format. The protocol for preparing the doses states that 6 vials (450 IU) were to be reconstituted in 1 mL 0.9% sterile saline and the final injection volume adjusted to 0.82 mL to achieve a 400 IU dose.

The difference between the US and EU formulations evaluated in this study was stated in the study report to be the polysorbate 20 content and the buffer, although the quantum of the difference was not specified. It should also be noted that the drug substance was reconstituted in 0.9% saline, whereas preserved (m-cresol) Water for Injections is provided with the currently proposed formulation.

Overall, the findings do suggest that the US formulation might, at least under the conditions of this study, yield slightly less FSH exposure but the difference is not clinically important as the dosage is in practice individually titrated. The outcome is not particularly relevant to the Australian application but does, taken together with the findings of study CS 05 above, provide further evidence that bioavailability of FSH from Menopur may be sensitive to minor formulation changes.

### **Study 2000-03**

**Study 2000-03** was included as a further pharmacokinetic study which examines, in a four way crossover design, the differences between intramuscular and subcutaneous administration and between conventional and highly purified preparations of menotrophin (*Repronex* brand name). This study, conducted in between January 2001 and May 2001 at three US sites, involved 33 healthy females, aged between 18 and 38 (mean 31) years, weight 47-81(mean 65) kg, randomised into 4 groups (8, 8, 8, 9 subjects) each given 225 IU Repronex, standard or purified preparation in random order, on Days 1, 8, 15, followed by six daily doses of 150 IU on Days 16 to 21 in the third phase. In Phase 1 (Day 1) two groups were dosed subcutaneously, one with Repronex and the other with purified Repronex and the other two groups received the same two treatments by intramuscular injection. For Phase 2 (Day 8) each group maintained the same dosing

route but received the alternate product. In Phase 3 (Days 15-21), all groups received purified Repronex, but by the dosing route alternate to that with which they had been dosed in the earlier phases.

It was clear to the evaluator that its data could not be used to formally demonstrate bioequivalence between Repronex and purified Repronex. In fact, no difference was observed between the profiles of these two products in any of the phases. In any case, this was not an issue for the Australian application in which purified Menopur (Repronex) is not being compared with a predecessor, less highly purified formulation. What is relevant is the comparison between SC and IM injection of the purified product, as the proposed Product Information (PI) allows for either form of administration as a matter of choice.

The complexity of the protocol used in the study makes comparison of the SC versus IM administration routes difficult and the study report reaches no firm conclusion in this regard. However, the data suggest that SC administration is no less effective than IM, may be more effective, and gives rise to no more variance in pharmacokinetic response.

### **Conclusion on pharmacokinetics**

1. There is an appropriate rise in FSH levels following administration of Menopur, which is reasonably consistent between the single and multiple dose formulations included in the application.
2. LH activity in the formulations is not confirmed by the included pharmacokinetic studies. The study reports attribute this, at least in part, to technical failure of the LH assay systems used but a more plausible explanation would be that the LH activity in the preparation is attributable to its content of hCG which was readily measured in study CS05. This would be consistent with the description in the PI that most of the product's LH content is in the form of hCG, and the explanation in one of the references that LH molecules are preferentially lost in the purification process.<sup>5</sup>
3. On the basis of pharmacokinetic assessment, SC administration of the product appears to suffer no disadvantage by comparison with IM, and may even be more effective.
4. It is possible that variation in the content of the excipients may have some effect on the pharmacokinetic properties of Menopur.

### **Pharmacodynamics**

No specific pharmacodynamic studies were included in the application, although some of the parameters measured in the clinical studies, for example, morphological evidence of follicular development and measurement of plasma oestradiol, reflect the mechanism of action of the two gonadotrophins contained in Menopur, FSH and LH.

Some comment was considered necessary by the evaluator about the balance of FSH and LH activity in Menopur, with particular regard to how much of the LH activity is attributable to the presence of human chorionic gonadotropin (hCG) and the source of the hCG activity in the preparation.

In normal physiology, the predominant gonadotrophin secretion by the pituitary in the early (follicular) phase of the menstrual cycle is FSH. A surge of LH secretion is associated with the process of ovulation in mid cycle and thereafter both FSH and LH levels are maintained, the role of LH being particularly to maintain progesterone production by the corpus luteum. If fertilisation and implantation occur, production of hCG commences and

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<sup>5</sup> Wolfensohn C, Grossman J, Coutu A et al. Batch-to-batch consistency of human-derived gonadotrophin preparations comparing with recombinant preparations. *Reproductive Biomedicine Online* 2005; 10: 442-454.

takes over this role as its actions are very similar to those of LH. Conventionally, hCG has been regarded as a hormone characteristic of and exclusively produced by chorionic tissue and as such its measurement in plasma and urine samples is used in the diagnosis of pregnancy and pregnancy associated pathology (hydatidiform mole and choriocarcinoma). However, it is now known that small amounts of hCG are produced by the pituitary along with LH and FSH.<sup>6,7,8</sup>

With the onset of ovarian failure at menopause, production of inhibin and oestradiol falls, reducing the negative feedback on the pituitary so that FSH and LH production rises. These hormones appear in increased quantities in the urine, hence the use of postmenopausal urine as a source of therapeutic gonadotrophin.

The information submitted for this evaluation creates some confusion regarding the nature and quantity of hCG activity in Menopur. The development of gonadotrophin preparations is summarised in the introductory section of the clinical evaluation report for the original application. This states that "menopausal gonadotrophin preparations typically contain FSH and LH activity in a ratio of 1:1, although some of the LH activity may be derived from added hCG". In describing the formulation, the report goes on to say that there is no mention of added hCG to standardise LH activity, but refers to references which suggest that hCG is routinely included in gonadotrophin preparations, with one reference specifically reporting measurement of hCG in Menopur.

It seems, in principle, unlikely that the pituitaries of multiple postmenopausal women would manage between them to produce FSH and LH in exactly equal amounts in the source material for Menopur and therefore plausible that the LH activity might be standardised by the addition of hCG, a substance readily available from biological sources, so as to achieve the 1:1 ratio suggested by the product description. However, the product information (PI) for the current application gives no such impression, clearly stating that there are equal international unit (IU) amounts of FSH and LH activity in each of the formulations and mentioning no source of the material other than the urine of menopausal/postmenopausal women. The PI goes on to say that hCG, which it describes as a naturally occurring hormone in postmenopausal urine, is the main contributor of the LH activity in the preparation. This is a surprising statement, as literature evidence suggests that hCG is produced by the pituitary in only small amounts, and there would seem no *a priori* reason to suspect that its proportional production would particularly increase after menopause.<sup>7,8</sup>

Some resolution to this paradox is provided by Wolfensohn et al.<sup>5</sup> This publication is a summary of studies done on composition and batch to batch consistency of gonadotrophin preparations conducted since the original application to TGA for Menopur; it should be noted that one of the authors (Couto) is a Ferring employee. Key points in the article are that:

(a) the source material for Menopur (and Bravelle, a similar product) is derived from more than 100,000 donors, each contributing urine several times. The consistency of starting material thus generated helps minimise batch to batch variation.

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<sup>6</sup> Cole LA, Gutierrez JM. Production of human chorionic gonadotropin during the normal menstrual cycle. *J Reprod Med* 2009; 54: 245-50.

<sup>7</sup> Birken S, Maydelman Y, Gawinowicz MA, Pound A, Liu Y, Hartree AS. Isolation and characterization of human pituitary chorionic gonadotropin. *Endocrinology* 1996; 137: 1402-11.

<sup>8</sup> Cole, LA, Sasaki, Y, Muller, CY. Normal production of human chorionic gonadotropin in menopause. *N Engl J Med* 2007; 356: 1184.



(b) during the purification procedure, FSH and LH bioactivities are fractionated, enabling adjustment of the added amounts so as to achieve a 1:1 ratio for FSH:LH in the final Menopur product.

(c) Menopur formulations are filled by international unit (bioactivity) rather than mass amounts and products using this method of quantification exhibit less variability.

(d) evidence is presented that the proportions of hCG by comparison with LH immunoreactivity vary considerably between HMG preparations and that Menopur contains a particularly high proportion of hCG (hCG: LH approximately 20:1). A particularly important statement in the discussion section, referenced to "internal data", is that LH molecules are preferentially lost compared with hCG during the purification procedure. This provides some explanation for the high hCG content of the final preparation although the extent of loss of LH remains surprising.

It should be noted that differentiation of hCG from LH can only be achieved by measurement of immunoreactivity, as their biological activity is similar, involving interaction with the same receptor.

Whether the exact proportions of FSH and LH (or hCG) activity in Menopur and similar preparations is of importance in relation to their clinical use is another question, and is discussed in following sections of this report.

## Efficacy

### Introduction

The efficacy data in the original application included one major study (MFK/IVF/0399E) which compared the efficacy and safety of Menopur versus Gonal-f (follitropin alfa) for controlled ovarian hyperstimulation (COH) in patients undergoing in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI). This was reviewed in detail in the clinical evaluation report for that application. The outcome of the study was that Menopur was not inferior to Gonal-f for the stated indication. The findings were subsequently published by the European and Israeli study group (EISG).<sup>9</sup> A sub analysis of the data, reproduced in Table 8, showed some evidence that Menopur might be specifically more effective in those patients having the treatment as part of an IVF program, as opposed to ICSI. The sponsor suggested that the former group present with female fertility issues, whereas the indication for ICSI is usually to do with male fertility and are therefore a different target group who may have improved responsiveness to a preparation with combined FSH/LH content as opposed to FSH alone.

**Table 8: Sub-analysis from Study MFK/IVF/0399E**

	IVF			ICSI		
	MENOPUR	rFSH	P value	MENOPUR	rFSH	P value
Number of patients	121	112	–	237	221	–
Positive beta-hCG	48 (40%)	30 (27%)	0.035	71 (30%)	70 (32%)	NS
Clinical pregnancy	42 (35%)	22 (20%)	0.009	56 (24%)	55 (25%)	NS
Ongoing pregnancy	38 (31%)	22 (20%)	0.037	49 (21%)	50 (23%)	NS

<sup>9</sup> The European and Israeli Study Group on highly purified HMG versus rFSH. Efficacy and safety of highly purified menotrophin versus recombinant follicle-stimulating hormone in *in vitro* fertilisation/intracytoplasmic sperm injection cycles: a randomised, comparative trial. *Fertil Steril* 2002; 78: 520-528.

These data do indicate an improved outcome in terms of achieving pregnancy with Menopur as opposed to rFSH in a COH protocol. However, the original clinical evaluation report recommended, in line with the findings of the study report itself, that the above data be interpreted "with caution", in view of the relatively small numbers and borderline levels of significance. The sponsor has gone on to coordinate a further large randomised controlled trial (RCT), conducted by essentially the same investigators comprising the EISG, in which the subjects were all undergoing IVF as opposed to ICSI. This is presented below as study CS003, the pivotal evidence for this aspect of the application. Additionally, the sponsor presented an integrated analysis of these two studies which comprises all of the evidence available to it regarding a direct comparison of Menopur with Gonal-f for this indication.

Finally, study CS002 was included as further evidence supporting the use of Menopur for ovulation induction in anovulatory females, an indication for which lower doses of gonadotrophin are used. Specific evidence using this formulation to support this indication was not provided in the original application.

### Study CS003

**Study CS003** was a large randomised, open label, assessor blind, parallel group, multicentre superiority study comparing highly purified menotrophin (Menopur) with the recombinant FSH (rFSH) preparation Gonal-f. Gonal-f is an existing product registered in Australia for indications similar to those submitted in this application. The study, conducted in 2004 in 37 European and Israeli centres, bears the acronym MERIT (**m**enotrophin vs **r**ecombinant FSH **i**n vitro fertilisation **t**rial), and has been the subject of several publications including one describing the clinical outcome.<sup>10</sup> The primary objective of the study was to establish superiority of Menopur compared to Gonal-f with respect to ongoing pregnancy rate in women undergoing IVF following down regulation with a GnRH agonist in a long controlled ovarian hyperstimulation (COH) protocol. Secondary objectives were to compare the two treatments with respect to a variety of parameters including biochemical and clinical indicators of ovulatory response and other clinical parameters of efficacy and safety.

The subjects were females, mostly Caucasian, aged 21-37 years with subfertility of a type qualifying for IVF treatment and evident for at least 12 months except in the case of proven bilateral tubal disorder. A total of 821 subjects were screened and 731 randomised, 363 to treatment with Menopur and 368 to Gonal-f.

The pituitary down regulation protocol employed triptorelin acetate administered on a continuous daily basis, 0.1 mg/day SC, starting 5-7 days prior to the next due menstrual period and continuing until the end of gonadotrophin (test or reference product) administration.

The COH protocol specified a starting dose of 225 IU for the first five days after which the dose was adjusted according to the subject's ovarian follicular response, with dosage adjustments to be changed by 75 IU at intervals of not less than 4 days. The 75 IU presentation was used throughout for both test and reference treatments; note that all doses are multiples of 75 IU. hCG (recombinant chorionic gonadotropin alfa, 250 µg SC, brand Ovitrelle) was given to induce follicular maturation once 3 or more follicles of  $\geq 17$  mm diameter were evident on transvaginal ultrasound; oocyte retrieval took place  $36 \pm 2$  hours later. Embryo assessment procedures and the remainder of the clinical protocol

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<sup>10</sup> Nyboe Andersen A, Devroey P and Arce J-C for the MERIT (Menotrophin vs Recombinant FSH in vitro Fertilization Trial) Group. Clinical outcome following stimulation with highly purified hMG or recombinant FSH in patients undergoing IVF: a randomised assessor-blind controlled trial. Hum Reprod 2006; 21: 3217-3222.

were consistent with usual ART practice. One or two embryos of defined quality were transferred on Day 3 after oocyte retrieval and progesterone as vaginal gel 90 mg/day was given for luteal support from the day of transfer until confirmation of clinical pregnancy 5-6 weeks after transfer, or a negative hCG pregnancy test 13-15 days after transfer. Follow up continued until confirmation or otherwise of ongoing pregnancy 10-11 weeks after transfer.

The study protocol specifies collection of information on pregnancy outcome in relation to delivery and neonatal health. This is included in the study report. The protocol also includes the option for the subjects to have subsequent transfer of frozen embryos; this data remained under collection at the time of report and was to be reported subsequently.

### **Statistical considerations**

The primary objective was to show that Menopur was superior to rFSH (Gonal-f) with respect to ongoing pregnancy rate. Testing was based on the likelihood ratio test in a logistic regression analysis, expressed as odds ratios with 95% CI and corresponding p values. The study was powered to detect an odds ratio of 1.67 for Menopur versus Gonal-f, requiring an ongoing pregnancy rate of 32% for Menopur and 22% for Gonal-f with 304 subjects in each group.

Provision was made for noninferiority testing in the event that superiority was not detected, based on a predefined noninferiority limit of 0.65 for the odds ratio of Menopur versus Gonal-f. The provision to switch from superiority to noninferiority is, as stated in the report, compliant with the TGA-adopted EU guideline.<sup>11</sup> Discussion of the study report does not provide justification for the noninferiority limit of 0.65 which could be regarded as rather generous. After review of the statistical analysis plan, the evaluator concluded that the selection of the margin of 0.65 appears to represent a compromise between a clinically satisfactory outcome and the impact of likely statistical variation. Had the trial data required close comparison with this margin, the robustness of its findings may have been in question. As the findings turned out, this was not the case. The finding of noninferiority was supported.

### **Results**

Details of the statistical analysis for the principal efficacy parameter in the "intent to treat" (ITT) population are shown in Table 9.

**Table 9: Ongoing pregnancies**

Ongoing pregnancy						Treatment effect*	
Menopur			Gonal-F			Menopur vs. Gonal-F	
N	n	%	N	n	%	Odds Ratio [95% CI]	P-value
363	97	26.7%	368	82	22.3%	1.25 [0.89 ; 1.75]	0.204

\* Treatment effect adjusted for age strata using a logistic regression analysis. P-value corresponds to likelihood ratio test.  
N = Number of subjects, n = Number of responding subjects, % = Response Rate

<sup>11</sup> EMEA, Committee for Proprietary Medicinal Products (CPMP), 27 July 2000. Points to Consider on Switching between Superiority and Noninferiority, CPMP/EWP/482/99.

There is a trend towards an improved ongoing pregnancy rate in the Menopur versus rFSH subjects (27% vs 22%), but this does not achieve statistical significance to show superiority as outlined above. Criteria for noninferiority were readily met, as the lower bound of the 95% CI (0.89) is well above the pre-specified noninferiority limit of 0.65.

A similar analysis for the “per protocol” (PP) population showed very similar results. Comparison of outcomes in younger (aged <35 years), who represent the majority, again showed a trend in favour of Menopur which came closer to achieving statistical significance (p= 0.82)

The number of embryos transferred was the same for both groups (1.7±0.5).

In subjects treated with Menopur, FSH concentrations were statistically significantly higher at all time points. There was no difference in LH concentrations between the treatment groups, consistent with the failure to demonstrate LH by immunoassay in subjects receiving Menopur in pharmacokinetic study CS05. Oestradiol levels were higher in the reference treatment group on Day 6 but higher in the Menopur group at the end of stimulation and at the time of oocyte retrieval. Levels of androgenic hormones were higher in the Menopur treated group. Intrafollicular levels of FSH, LH, hCG and oestradiol were statistically significantly higher in Menopur treated subjects. Levels of other hormones including inhibin A and B, IGF-I, VEGF and hydrocortisone showed a variable pattern of no apparent significance.

Subjects treated with Menopur, by comparison with those on the reference treatment, required a higher overall dose (2508 versus 2385 IU), a higher daily dose (238 versus 233 IU) and a longer duration of treatment (10.4 to 10.1 days). Somewhat surprisingly, these changes which are in the 2-5% range, achieve statistical significance but the quantum of difference has no real impact and would be particularly unimportant if on further evaluation the possible improvements in pregnancy outcome turned out to be a real finding.

### **Study CS002**

**Study CS002** was a randomised, open label, assessor blind, parallel group, multicentre study designed to establish noninferiority of Menopur by comparison with rFSH (Gonal-f), using a chronic low dose step up protocol in women with anovulatory infertility who had failed clomiphene treatment. It was carried out between May 2003 and June 2004 in 8 Belgian, 7 UK, 5 Swedish and 9 Danish sites.

The subjects were females aged 18-39 years with a minimum one year history of infertility. To qualify for enrolment, women had to have a history of spontaneous or induced menstrual bleeding and to have either failed to ovulate with incremental doses of clomiphene citrate at 100 mg/day for five days, or to have failed to conceive after three cycles of ovulation induction with clomiphene. Of 229 women screened, 184 were randomised, 91 to Menopur, and 93 to rFSH. The mean age of the subjects was 29 years in both groups and there was a significant incidence of increased body weight, mean BMI being 26.5 kg/m<sup>2</sup> in the Menopur treated subjects and 25.0 kg/m<sup>2</sup> in the rFSH group; this reflects the background pathophysiology of anovulatory infertility. In this context it is important to observe that there were no clinically meaningful differences in serum levels of LH, FSH, LH/FSH ratio, oestradiol or progesterone at baseline

Gonadotropin (test or reference) was started at 75 IU daily, 2-5 days after a spontaneous or progestogen induced menstrual period. Response was assessed by individual investigators with transvaginal ultrasound as is standard practice. A decision was made every 7 days as to whether to maintain the daily gonadotropin dose or increase it by 37.5 IU daily; an increase was deemed necessary if a follicle of 10 mm or more diameter was

seen on ultrasound. Treatment was continued for a maximum of 42 days and up to a maximum daily dose of 225 IU. Once a predefined level of ovarian response was observed, 5000 IU hCG (Profasi brand) was given either SC or IM, again in line with usual practice. Ovulation was determined by measurement of serum progesterone. Luteal support was not permitted. Diagnosis of biochemical pregnancy was achieved by measurement of serum hCG 12-16 days after hCG administration, and clinical and ongoing pregnancy confirmed by transvaginal ultrasound at Weeks 7 and 12.

The primary efficacy parameter was the ovulation rate in the two treatment groups. Ovulation was defined as a mid-luteal serum progesterone concentration of  $\geq 25$  nmol/L, or the presence of clinical pregnancy at Week 7. Secondary objectives of the study were comparison between the treatment groups of biochemical, clinical and ongoing pregnancy rates, biochemical and morphological indices of ovarian follicular development, endometrial status, total gonadotropin dose used and the threshold dose of gonadotropin required for ovulation.

### ***Statistical considerations***

The investigators anticipated an ovulation rate of approximately 80% with a true difference between the treatments of zero. The selected noninferiority margin was 20%, so that to establish noninferiority, the lower limit of the two sided 95% CI for the difference between the two treatments should be  $>$  minus 20%. This margin, being 25% of the established treatment effect, is appropriate. On this basis, it was calculated that 63 patients in each treatment group would be required to determine noninferiority with 80% power.

All randomised patients received at least one dose of study medication and the ITT population was 100% of the 184 subjects randomised; these also constitute the safety population. The PP population comprised 70/91 (76.9%) of those randomised to Menopur and 83/93 (89.2%) of those randomised to rFSH.

### ***Results***

The statistical analysis for the primary efficacy parameter, ovulation rate, are shown below both for the PP population (upper panel), regarded by the investigators as primary, and the ITT population (lower panel):

**Table 10: Ovulation rate**

	MENOPUR	GONAL-F	Treatment difference (%) (95% CI)*
	N (%)	N (%)	
FP Analysis set	70	83	
Ovulation			
YES	60 ( 85.7%)	71 ( 85.5%)	0.17 (-11.0 - 11.33)
NO	10 ( 14.3%)	12 ( 14.5%)	

N : Number of subjects

% : Percentage of subjects

\* : Estimated in a Generalised Linear Model using a binomial distribution with the identity link function. The two-sided 95% CI was calculated using the normal approximation to the estimated difference in proportions.

	MENOPUR	GONAL-F	Treatment difference (%) (95% CI)*
	N (%)	N (%)	
ITT Analysis set	91	93	
Ovulation			
YES	76 ( 83.5%)	79 ( 84.9%)	-1.43 (-12.0 - 9.10)
NO	15 ( 16.5%)	14 ( 15.1%)	

N : Number of subjects

% : Percentage of subjects

\* : Estimated in a Generalised Linear Model using a binomial distribution with the identity link function. The two-sided 95% CI was calculated using the normal approximation to the estimated difference in proportions.

For both analyses, the ovulation rates are closely similar between the treatment groups and above the 80% level predicted. The lower bound of the 95% CI is in each case well above the level of minus 20% required for demonstration of noninferiority.

Further analyses of the ovulation rate were performed adjusting for subject age and body weight. The results were closely similar to the main analysis, suggesting that the finding of noninferiority is uninfluenced by and independent of age and body weight. This finding is relevant to the reliability of the study findings, as there was some misdistribution of subjects by body weight, 30% in the Menopur group meeting the criterion for obesity of BMI  $\geq 30$  kg/m<sup>2</sup>, compared with 15% in FSH group.

The proportion of subjects achieving biochemical, clinical and ongoing pregnancy was closely similar between the treatment groups whether assessed on the basis of the PP or ITT population, as shown in Table 11:

**Table 11: Biochemical, clinical and ongoing pregnancies**

	PP Population		ITT Population	
	MENOPUR (N=70)	GONAL-F (N=83)	MENOPUR (N=91)	GONAL-F (N=93)
Positive $\beta$ hCG	17 (24.3%)	17 (20.5%)	20 (22.0%)	19 (20.4%)
Clinical pregnancy (7 $\pm$ 2 weeks after hCG)	14 (20.0%)	15 (18.1%)	14 (15.4%)	17 (18.3%)
Ongoing pregnancy (12 $\pm$ 2 weeks after hCG)	13 (18.6%)	14 (16.9%)	13 (14.3%)	16 (17.2%)

Statistical analyses were performed for all of the parameters of pregnancy outcome and for the other secondary outcomes including various indices of follicular development and endometrial thickness. No differences were identified by treatment group and the ratio of means was close to unity for all parameters, with similar confidence intervals as shown for the primary efficacy parameter.

With regard to gonadotropin dosage, there was (as in study CS003) a trend towards longer duration of treatment and higher total dosage in the Menopur group; the average duration of treatment for Menopur subjects was 15.3 $\pm$ 7.9 days, compared with 12.0 $\pm$ 5.0 days for FSH. Corresponding total gonadotropin doses were 1491 $\pm$ 1177 IU for Menopur and 1022 $\pm$ 580 IU for FSH. These differences did not, however, reach statistical significance (p-values 0.097 and 0.086 respectively). The median threshold dose for ovulation was 75 IU in both treatment groups.

The overall findings of this study strongly support the noninferiority of Menopur by comparison with rFSH for the OI indication; criteria for equivalence may well have been met but were not examined.

### Integrated analysis

This report was presented as an integrated evaluation of "all completed and reported Phase III RCTs comparing Menopur with rFSH"; in fact, comprising the two trials MFK/IVF/0399E and CS003 evaluated by the TGA in this and the previous clinical evaluation report. This is justified in the report as representing a larger exposure (1458 patients) than the existing available Cochrane database comparing menotrophins and rFSH which comprised 1214 patients, including those of study MFK/IVF/0399E.<sup>12</sup> Although this approach is selective for the sponsor's own product, it does enable a robust analysis as the two trials are very similar in terms of patient selection and clinical protocol and as the study report points out, the dataset represents approximately 75% of the evidence available at the time from RCTs comparing menotrophin with FSH in long GnRH agonist protocols.

The integrated population is described in Table 12.

<sup>12</sup> Van Wely M, Westergaard LG, Bossuyt PMM, Van der Veen F. Human menopausal gonadotropin versus recombinant follicle stimulation hormone for ovarian stimulation in assisted reproductive cycles (Cochrane review). In: the Cochrane library, Issue 1, 2003. Oxford: Update Software.

**Table 12: Description of populations**

Study	IVF	ICSI	Total
FE999906 CS003	731	0	731
MFK/IVF/0399E	255	472	727
Total	986	472	1458

**Results for IVF subjects**

The statistical analysis for IVF subjects was conducted on the ITT population (n= Menopur 491, Gonal-f 495). The safety population was identical. There were 60 withdrawals in the Menopur and 72 in the Gonal-f group, so the completion rates were 88% and 85% for the two groups respectively. The reasons for withdrawal were similar in the two groups with protocol non-compliance being the most common in each.

The demographic characteristics for the two populations were obviously similar to those of the constituent studies which have already been reviewed in this and the previous clinical evaluation and the test and reference groups are essentially identical in all characteristics.

There was a wide variety of reasons for infertility in the study population. In the Menopur group, 37% were classified as tubal infertility, 7% had endometriosis and 15% were classified as "male factor". Only 4% had ovulatory disorders and 38% were categorised as unexplained. The proportions in the comparator group were similar.

Most included subjects (70% Menopur, 66% comparator) were naive to ART treatments.

The principal efficacy outcome described in this report is live birth resulting from the treatment. The use of this parameter is justified by the discussion and recent literature references. It is certainly the outcome most desired by patients undergoing this treatment. The results show a significant treatment effect in favour of Menopur and are shown in Table 13.

**Table 13: Live births**

Live birth						Treatment effect*	
Menopur			Gonal-F			Menopur vs. Gonal-F Odds Ratio [95% CI]	P-value
N	n	%	N	n	%		
491	130	26.5%	495	103	20.8%	1.36 [1.01 ; 1.83]	0.041

\* Treatment effect adjusted for age and study using a logistic regression analysis. P-value corresponds to likelihood ratio test.

N = Number of subjects, n = Number of responding subjects, % = Response Rate

No difference was observed in the proportion of live births by number of oocytes retrieved.

The live birth rate per IVF cycle with embryo transfer was 32% for Menopur versus 25% for rFSH. This was also statistically significant (p= 0.034) with an odds ratio of 1.39 (95% CI 1.03-1.89).

The birth rate results were additionally stratified by age, with a cut-off point of 35 years as in study C003. There was a trend towards a higher live birth rate per started IVF cycle



with Menopur versus FSH in the younger population (28% to 22%) but this failed to achieve significance ( $p=0.060$ ).

Similar analyses were performed using the parameter of ongoing pregnancy, which has been the primary criterion of efficacy in many ART studies including CS003 as evaluated above. The comparison had similar results to that for live birth and again achieved statistical significance as shown in Table 14.

**Table 14: Ongoing pregnancies**

Ongoing pregnancy						Treatment effect*	
Menopur			Gonal-F			Menopur vs. Gonal-F	
N	n	%	N	n	%	Odds Ratio [95% CI]	P-value
491	134	27.3%	495	105	21.2%	1.38 [1.03 ; 1.86]	0.030

\* Treatment effect adjusted for age and study using a logistic regression analysis. P-value corresponds to likelihood ratio test.

N = Number of subjects, n = Number of responding subjects, % = Response Rate

In this analysis, a relationship was established in relation to oocyte retrieval; in subjects with at least 4 oocytes retrieved after treatment, ongoing pregnancy was more likely (29%) when the treatment had been Menopur then when rFSH had been used (23%,  $p=0.031$ ), odds ratio 1.39 (95% CI 1.03-1.88). Ongoing pregnancy was also more likely when examined per IVF cycle with embryo transfer (33% Menopur, 25% rFSH) and in patients <35 years of age (Menopur 29%, rFSH 23%,  $p=0.042$ ).

Similar results with odds ratios in the range 1.33-1.46 were found with regard to the parameters clinical pregnancy rate, implantation rate, and ongoing implantation rate.

The numbers of oocytes retrieved per IVF cycle was greater with rFSH (12.3+6.7) than with Menopur (10.5+5.9;  $p<0.001$ ). The fertilization rate was 54% for both treatment groups.

Average treatment duration with Menopur was 10.7+1.9 days and with FSH it was 10.5+1.9. The difference of 0.2 days appears trivial but was statistically significant ( $p=0.033$ ). Total gonadotrophin usage was 2593 +768 IU for Menopur and 2476+689 IU for FSH. Again this difference, while of dubious clinical significance, was statistically significant ( $p=0.006$ ).

There was no analysis of outcome in relation to cause of infertility.

Per IVF cycle, subjects stimulated with Menopur as opposed to FSH had a statistically significantly higher chance of a singleton live birth (19% versus 15%,  $p=0.047$ ). Singletons accounted for 73% of the live birth cycles with Menopur and 70% with FSH, and twins 26% and 30% respectively; there was a single set of triplets born to a Menopur subject.

Other aspects of pregnancy outcome including gestational age at delivery, birth weight, gender balance, and incidence of congenital anomalies, showed no difference between the two groups.

### Subjects undergoing ICSI

Similar comparative analyses to those described above were carried out on the dataset of subjects undergoing ICSI (ITT population: Menopur 245, rFSH 227). No statistically significant differences in any of the parameters were observed and inspection of the data

by the evaluator also revealed no trends to such differences as were observed in the population undergoing IVF. It was not felt necessary to provide a detailed review of this data.

### **Summary on efficacy**

For the COH indication, the pivotal trial CS003 failed to show superiority of Menopur over rFSH in terms of a treatment effect on pregnancy outcome. Such an effect is, however, supported by the integrated analysis of trials MFK/IVF/0399E and CS003 which shows a statistically significant treatment effect of Menopur on a number of outcome parameters including ongoing pregnancy and live birth rate. The level of significance is relatively low, with p-values in the range 0.02-0.05 but the quantum of change is clinically valuable with ongoing pregnancy and live birth rate in the range 25-30% higher than in patients treated with rFSH.

With regard to the OI indication, trial CS002 amply demonstrates noninferiority of Menopur with respect to rFSH and supports this treatment being of equal clinical value to rFSH, with no particular advantage being suggested or claimed.

### **Safety**

All treatment programs involving the administration of gonadotrophins for female infertility carry the expectation that there will be an incidence of adverse effects attributable to the supraphysiological doses of hormones used. In particular, an incidence of ovarian hyperstimulation syndrome (OHSS) can be anticipated despite the reduction in the frequency of its occurrence with modern treatment protocols. The focus of safety assessment in this evaluation will therefore be not so much the observation of whether OHSS and related adverse effects (AEs) occur but rather the frequency of these AEs in the test versus reference populations of the included data and the need to demonstrate that the proposed new treatment (Menopur) does not carry an increased risk in this regard.

In CS003, the overall incidence of adverse events (AEs) was similar in the two treatment groups (51% vs 49%). There were no unusual or unexpected events and no deaths occurred during the study. OHSS occurred in 13 subjects in the Menopur group (4%) and 10 in the rFSH group (3%). Of these, 8 cases in each group were in the moderate/severe category. There was no difference evident between the groups in the timing of onset of these cases.

In CS002, the overall incidence of AEs was similar in the two treatment groups (41%, 40%), without any unusual or unexpected pattern. There were no deaths. OHSS occurred in 1 Menopur subject and 3 rFSH subjects.

In the safety analysis for the integrated analysis, there were no differences in any of the AE parameters examined. In particular, moderate or severe OHSS, the incidence of which tends to reflect the level of FSH/oestrogen exposure, occurred in the same number of subjects (total of 9, 1.8%) in each group. Miscarriage and ectopic pregnancy occurred in similar numbers in each group. Further information comes from this analysis, the safety summary of which contains analyses of the database of 1458 subjects resulting from a combination of trials of CS003 and MFK/IVF/0399E. The overall pattern of adverse event reporting and OHSS incidence is described separately for the IVF cycle and ICSI cycle subsets in Tables 15 and 16 for IVF and Tables 17 and 18 for ICSI. From these it can be noted that there is no qualitative or frequency distribution pattern of AE reporting or OHSS incidence showing any difference between the treatment groups.

Table 15: IVF – adverse events reported at a frequency &gt;1%

MedDRA System organ class/ Preferred term	Menopur		Gonal-F	
Safety analysis set	491		495	
Any adverse events	259 (53%)	539	253 (51%)	527
<b>GASTROINTESTINAL DISORDERS</b>				
Nausea	17 (3%)	21	20 (4%)	26
Abdominal distension	12 (2%)	16	13 (3%)	16
Abdominal pain	11 (2%)	12	10 (2%)	10
Diarrhoea	5 (1%)	5	4 (1%)	5
Vomiting	7 (1%)	7	1 (<1%)	1
<b>GENERAL DISORDERS AND ADMINISTRATION</b>				
<b>SITE CONDITIONS</b>				
Injection site erythema	8 (2%)	10	4 (1%)	7
Fatigue	2 (<1%)	3	8 (2%)	9
Injection site pain	8 (2%)	12	2 (<1%)	3
<b>INFECTIONS AND INFESTATIONS</b>				
Nasopharyngitis	4 (1%)	4	5 (1%)	5
<b>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</b>				
Post procedural pain	14 (3%)	14	19 (4%)	20
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>				
Back pain	3 (1%)	3	6 (1%)	7
<b>NERVOUS SYSTEM DISORDERS</b>				
Headache	50 (10%)	73	50 (10%)	76
Migraine	6 (1%)	8	3 (1%)	4
<b>PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS</b>				
Abortion spontaneous	22 (4%)	22	26 (5%)	26
Abortion missed	9 (2%)	9	7 (1%)	9
Ectopic pregnancy	3 (1%)	4	5 (1%)	5
<b>REPRODUCTIVE SYSTEM AND BREAST DISORDERS</b>				
Vaginal haemorrhage	89 (18%)	95	94 (19%)	97
Pelvic pain	21 (4%)	27	22 (4%)	26
Ovarian hyperstimulation syndrome	23 (5%)	24	17 (3%)	17
Adnexa uteri pain	7 (1%)	9	5 (1%)	5
Ovarian cyst	5 (1%)	6	4 (1%)	5
Dysmenorrhoea	2 (<1%)	2	6 (1%)	6
Breast pain	6 (1%)	6	1 (<1%)	1
Ovarian hyperfunction	2 (<1%)	2	5 (1%)	5

N = Number of subjects with adverse events  
(%) = Percentage of subjects with adverse events  
E = Number of Adverse Events

Table 16: IVF – OHSS

	Menopur	Gonal-F
Safety analysis set	491	495
Moderate/Severe OHSS	9 (1.8%)	9 (1.8%)

N = Number of subjects. % = Percentage of subjects

Table 17: ICSI – adverse events reported at a frequency &gt;1%

	Menopur		Gonal-F	
Safety analysis set	245		227	
Any adverse events	136 (56%)	478	133 (59%)	360
<b>EAR AND LABYRINTH DISORDERS</b>				
Vertigo	1 (<1%)	1	3 (1%)	3
<b>GASTROINTESTINAL DISORDERS</b>				
Abdominal pain	36 (15%)	55	34 (15%)	46
Nausea	27 (11%)	35	11 (5%)	16
Abdominal pain lower	11 (4%)	16	7 (3%)	12
Diarrhoea	6 (2%)	7	9 (4%)	11
Abdominal distension	8 (3%)	10	6 (3%)	8
Vomiting	5 (2%)	6	5 (2%)	5
Abdominal discomfort	1 (<1%)	1	4 (2%)	4
Flatulence	3 (1%)	9	0	
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>				
Injection site pain	10 (4%)	18	7 (3%)	9
Injection site erythema	8 (3%)	12	5 (2%)	7
Pain	5 (2%)	5	2 (<1%)	2
Fatigue	2 (<1%)	3	4 (2%)	5
Injection site swelling	4 (2%)	8	2 (<1%)	3
Pyrexia	3 (1%)	3	2 (<1%)	3
<b>INFECTIONS AND INFESTATIONS</b>				
Nasopharyngitis	6 (2%)	6	8 (4%)	8
<b>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</b>				
Post procedural pain	14 (6%)	17	7 (3%)	7
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>				
Back pain	6 (2%)	7	3 (1%)	5
Pain in extremity	3 (1%)	4	1 (<1%)	1
<b>NERVOUS SYSTEM DISORDERS</b>				
Headache	66 (27%)	117	49 (22%)	73
Dizziness	6 (2%)	6	3 (1%)	3
Migraine	4 (2%)	6	0	
<b>PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS</b>				
Abortion missed	4 (2%)	4	2 (<1%)	2
Ectopic pregnancy	3 (1%)	3	1 (<1%)	1
Abortion spontaneous	0		3 (1%)	3
<b>REPRODUCTIVE SYSTEM AND BREAST DISORDERS</b>				
Ovarian hyperstimulation syndrome	18 (7%)	20	14 (6%)	17
Vaginal haemorrhage	7 (3%)	12	11 (5%)	13
Adnexa uteri pain	2 (<1%)	2	4 (2%)	7
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>				
Pharyngolaryngeal pain	5 (2%)	5	3 (1%)	4
Cough	3 (1%)	3	1 (<1%)	1
<b>VASCULAR DISORDERS</b>				
Haematoma	1 (<1%)	1	3 (1%)	3
Hot flush	3 (1%)	4	1 (<1%)	2
Orthostatic hypotension	3 (1%)	3	1 (<1%)	2

N = Number of subjects with adverse events  
 (%) = Percentage of subjects with adverse events  
 E = Number of Adverse Events

Table 18: ICSI – OHSS

	Menopur	Gonal-F
Safety analysis set	245	227
Moderate/Severe OHSS	5 (2.0%)	2 (0.9%)
N = Number of subjects, (%) = Percentage of subjects		

## **Postmarketing Data**

The submission included five submitted Periodic Safety Update Reports (PSURs) that estimate current cumulative worldwide use of Menopur at 1.1 million treatment cycles and of Ferring brand menotrophin overall at 3.1 million treatment cycles in 1.2 million patients.

Estimates of AE incidence from these data rely on spontaneous reporting and provide no comparison with any other product. The most recent PSUR (January-December 2008) describes 26 individual adverse drug reaction (ADR) reports identified as being of particular interest, including 10 cases of OHSS. Some of the latter appear to be attributable to inappropriate dosage protocol and the number described represents a very small fraction of the expected incidence from the described exposure to the product.

## **Summary on safety**

The submitted data revealed no new safety issues nor any evidence of adverse effects attributable to Menopur by comparison with the reference product (recombinant FSH, Gonal-f) employed in the studies containing the application. This conclusion is consistent with that of the original clinical evaluation.

## **Clinical Summary and Conclusions**

### **Preamble**

The clinical evaluation report for the original application which was in general favourable, identified a number of deficiencies. The sponsor's responses to these are commented upon as follows:

#### ***Satisfactory assessment of the FSH and LH content of Menopur***

The sponsor's response indicates that this had been addressed in the quality documentation, so it is presumed that this will be the subject of the evaluation of chemical issues. From the data available to the clinical evaluator, it seemed clear that there is very little LH in the product and that the luteinising activity is attributable to hCG of pituitary origin, as discussed in detail above under Pharmacodynamics. The draft PI actually contained a statement in its introductory paragraph that hCG of pituitary origin is "the main contributor of the LH activity".

#### ***Clarification of the hCG content in Menopur***

This has already been discussed above. In principle, the clinical evaluator saw a problem in the product being described as containing equal quantities of FSH and LH activity when the sponsor's own data suggests that it consists of FSH and pituitary derived hCG, with very little LH content at all. Perhaps it should be described as such.

#### ***Satisfactory risk assessment of Menopur with respect to TSEs (transmissible spongiform encephalophies)***

The sponsor's response indicates that this also has been addressed in the quality documentation. Nevertheless, no comment has been made in the draft PI and the question of a duty to inform about this issue is a clinical issue and is discussed further in the following section of this AusPAR.

## **General comments**

### ***Route of administration***

The draft PI and Consumer Medicines Information (CMI) both recommend that the product can be given by either SC or IM administration. Study 2000-03 does provide some evidence that there may be a subtle difference in the pharmacokinetic response

between the two routes of administration. It was noted in the pivotal efficacy study CS003, that SC administration was specified. SC injection is less painful and is simpler, particularly for self administration.

Given these factors, the clinical evaluator saw no basis for maintaining the option of IM administration as it appears less effective, is less convenient and is a factor that potentially could contribute to variation in response which can easily be eliminated.

### ***Menotrophin versus rFSH***

The key aspect of this application and the one which will influence its marketing and use in clinical practice, if approved, is the question of whether menopausal gonadotropin (Menopur) has any advantage over recombinant FSH, particularly in the COH setting, as opposed to being just an alternative therapy. At the time of the original application there was evidence of marginal significance to support the proposition, in the form of study MFK/IVF/0399E and also the Cochrane review.<sup>12</sup> The studies in the current application represent an attempt to provide certainty about this issue; they do not do so but do provide some further supporting evidence. It could reasonably be said that the question of an advantage of menotrophin over rFSH has moved from the realm of the possible to the probable. The original clinical evaluation report in a section headed "who should have HMG rather than FSH?", includes the following statement: "... *in choosing gonadotrophins for ART for individual patients or for treatment programs, clinicians will consider the broader information available and are likely to see some advantages in using HMG for at least some women.*" The clinical evaluator considered that this remains an accurate description of the current position.

In summary, as the quantum of data examined becomes larger, it increasingly seems that there may be an advantage to undertaking COH with menotrophin as opposed to FSH for women undergoing IVF cycles, but not ICSI. It would be easier to accept this as a real difference if there was a tenable hypothesis to explain it. The notion of the difference being attributable to the cause of infertility (male related in ICSI, female in IVF) is difficult to sustain as a high proportion of the IVF treatments relate to factors such as tubal interruption or male factor which have no connection with the target of the treatment: the ovulatory process. A more plausible explanation is provided in the discussion of the integrated analysis report, relating to a difference between the two fertilisation procedures. In IVF cycles, cumulus cells surround the oocyte for about one day after retrieval, whereas in the ICSI protocol they are stripped from the oocyte immediately after retrieval. A reference is given to a study supporting the role of cumulus cells in the differential effects of LH.<sup>13</sup>

### **Use in males**

The application includes no clinical data on males and the only support for this indication is a single sentence in the draft PI to the effect that efficacy and safety have been documented in the literature. The included references, however, do not include any on this subject. There is, in fact, documentation in the literature specifically regarding the use of human menopausal gonadotrophin as well as rFSH for induction of spermatogenesis.<sup>14,15</sup> The LH (or hCG) content of menotrophin would confer no particular advantage in this clinical situation as hCG is routinely given as initial treatment in patients

<sup>13</sup> Assou S, Anahory T, Pantesco V et al. The human cumulus-oocyte complex gene expression profile. Hum Reprod 2006, doi: 10.1093/humrep/de1065.

<sup>14</sup> Bouloux P, Warne DW, Loumaye E. Efficacy and safety of recombinant human follicle-stimulating hormone in men with isolated hypogonadotropic hypogonadism. Fertil Steril 2002; 77: 270-273.

<sup>15</sup> Finkel DM, Phillips JL, Snyder PJ. Stimulation of spermatogenesis by gonadotropins in men with hypogonadotropic hypogonadism. N Engl J Med 1985; 313: 651-5.

with secondary hypogonadism, with FSH being added if there is no response. There is no evidence that menotrophin would have an advantage over rFSH for this use, except for the possibility of an economic benefit in terms of the relative cost of the products.

### Conclusion

Subject to resolution of the various issues referred to above and within the limits of the available data, no objection was seen to registration on the grounds of acceptable efficacy and safety.

## V. Pharmacovigilance Findings

### Risk Management Plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR). The summary of the RMP is shown in Table 19.

**Table 19: Summary of the RMP**

<b>Important identified risks</b>	OHSS	Routine PhV
	Anaphylaxis	Routine PhV
<b>Important potential risks</b>	None	
<b>Important missing information</b>	Experience in people with hepatic or renal impairment	Routine PhV

In a clinical review of the safety specification, the clinical evaluator noted that the theoretical risk of transmission of infectious agents by this human derived product, specifically the incompletely identified agent responsible for spongiform encephalopathy (Creutzfeldt-Jakob disease [CJD]), is a difficult issue. On the one hand there is the factor that any mention of even a minimal risk of such a catastrophic potential AE would quite likely result in rejection of use of the product; while on the other there is some degree of "duty to warn". The RMP indicates that the sponsor finds it necessary to "source responsibly" in line with current guidance documents and also to adhere to the recommendations of the relevant EU position statement on the issue. Given this, the evaluator noted that infectious disease transmission, perhaps without necessarily mentioning Creutzfeldt-Jakob disease specifically, should be identified as an "important potential risk".

The OPR reviewer noted that there is extensive post market experience with menotrophin. The safety issues of OHSS and anaphylaxis have been well characterised and although there is missing information on use in individuals with hepatic or renal impairment, a review of postmarket safety data conducted by the sponsor found no evidence of a safety issue in this population.

For each of these safety issues the sponsor has proposed routine pharmacovigilance (PhV) with no additional pharmacovigilance activities.<sup>16</sup> Routine risk minimisation activities are proposed for the two identified risks, but not for the area of missing information.<sup>17</sup>

The following issues were identified by the reviewer:

1. The potential for overdose, misuse and off label use (including paediatric off label use) appear very low. However, it is still important that the sponsor has a surveillance process to monitor for these issues. Routine pharmacovigilance activities would be appropriate to monitor these issues and information gained from this surveillance could be communicated in the context of PSUR.
2. The potential for transmission of infectious agents remains unclear.
3. Routine risk minimisation (inclusion in the PI) is required for the area of important missing information, use in individuals with renal or hepatic impairment.
4. It was also recommended that all the risk factors for OHSS are included in the PI.

Overall, the submitted risk management plan was considered acceptable. Routine pharmacovigilance and risk minimisation activities were considered appropriate to monitor the safety issues identified.

## VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

### Quality

The sponsor withdrew the application to register the 75IU single dose vial during the evaluation phase.

### Biopharmaceutics

The bioavailability study (CS05) revealed bioequivalence of the two products in relation to FSH. It should be noted the 1200 IU formulation used in this study is different to that proposed for marketing. The product used had sodium chloride as an excipient and thus a higher osmolarity. The sponsor provided justification as to why this would not affect bioavailability. Whilst this justification is not entirely based on scientific evidence, the PI inclusion that individual titration is required based on response should address any potential to affect bioequivalence.

### Characterisation

There were significant outstanding issues relating to the characterisation of this product: this was the basis of the sponsor's withdrawal of the previous application. In that application, the following were identified as the minimum acceptable data that needed to

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<sup>16</sup> Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

<sup>17</sup> Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.



be provided in relation to characterisation (as the glycosylation profile was found to be inadequate):

- Glycosylation profiling of the purified active ingredient, final product and purified FSH with identification of the major peaks.
- Batch analysis of a minimum of three batches- oligosaccharide profiling providing numerical proportions of the peaks.
- Active ingredient and or final product specifications- an assay developed and validated to provide the glycosylation profile.

These issues were not satisfactorily addressed by the sponsor in the current application. The concerns as detailed by the evaluator in the present application are as follows:

1. There was an anomalous charge status of Menopur compared with published quantitation for pituitary derived gonadotrophins. Menopur had a significantly lower proportion of non- and mono- charged glycans and greater di- and tri-charged glycans. This was not satisfactorily explained. The sponsor maintained that the application is a “stand alone” product and that comparability to pituitary or other urinary gonadotropins is not required. The evaluator was of the opinion that, “as there is always a finite likelihood of a patient being switched from one gonadotropin preparation to another, the biological activities expressed as IU are what the dosage is based on ..... and the substitution (even if it be by selection during purification) of LH by hCG will lead to anomalously high (and undeclared) extended luteinising activity...”.

The evaluator was also not satisfied with the annual testing for glycosylation (against a reference testing standard) to be undertaken by the sponsor as it was thought that there was a potential for deficient batches to be missed.

2. There was concern whether Menopur conforms to the BP. The evaluator’s response was as follows :

“The company reiterated that the content of LH in Menopur is verging on zero and the luteinising activity is almost solely due to hCG. The BP/PhEur makes the allowance that *“where necessary, chorionic gonadotrophin obtained from the urine of pregnant women may be added to achieve the above ratio”*, but it was never the intent of the monograph that LH would be effectively replaced by hCG. As pointed out previously, hCG has a much longer circulatory half-life than LH. While hCG may have similar luteinising activity to LH, the pharmacokinetics of the luteinising activity of hCG is significantly different to LH. The luteinising activity is measured only by an *in vivo* assay in rats. This assay is a single endpoint assay after 3 injections designed to measure the activity of LH. Because of the longer half life of hCG, if the endpoint is taken later, the mass gain of the seminal vesicles of the rats is greater reflecting the extended total luteinising activity over the true half-life of the gonadotropin. For this reason, the two gonadotropins cannot be regarded as interchangeable. The evaluator maintained his opinion that this product does not conform to the monograph and cannot be termed “human menotrophin.”

The evaluator maintained that the substitution (even if it is by selection during purification) of LH by hCG will lead to anomalously high (and undeclared) extended luteinising activity. It is possible that glycosylation is likely to confer an inflated potency on the product which would exacerbate the longer half-life of the hCG.

The evaluator recommended rejection of the 600 IU and 1200 IU strengths as the product does not “conform to the BP leading to the possible extended luteinising activity and is anomalously glycosylated possibly leading to inflated potency”.

The Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) differed from the evaluator in the interpretation of the relevant BP monograph but was also unable to recommend approval on pharmaceutical grounds. It noted that “in particular, significant deficiencies were identified in the data submitted in relation to glycosylation/ characterisation of the products”.

### **Sterility**

The evaluator noted that pathogen safety questions have been adequately addressed. Viral validation studies were considered satisfactory and were conducted in accordance with the TGA-adopted EU guidelines.<sup>18,19</sup> However, the PSC “raised safety concerns about the collection of urine from such a large population. The PSC considers that such a large pool of urine may increase the potential for CJD contamination”.

The Delegate noted that the evaluator’s concerns regarding glycosylation were valid: a characteristic of gonadotropins is that the degree of glycosylation affects the potency and duration of response; the carbohydrate portion of the gonadotropins influence the folding, assembly, secretion, clearance and biological activity of the gonadotropins. However, it was considered that it is not satisfactory to claim this is a “stand-alone” product which will not be interchangeable with other gonadotropins as “off-label” use cannot be prevented.

There remained an unresolved issue regarding the quality of the product. In regard to sterility, it was stated that viral validation studies were considered satisfactory and were conducted in accordance with the TGA-adopted guidelines. However, the consequent relevance of risk reduction is difficult to assess especially as there are published papers that report prions in the urine and there are insensitive assays to detect these.

### **Nonclinical**

The nonclinical evaluator noted that data submitted addressed the deficiencies of the original application. The original data set included local tolerance studies and did not include efficacy studies or toxicity studies. The evaluator of that application recommended rejection.

The current dataset included a repeat dose toxicity study, local tolerance studies and an expert statement justifying the absence of an allergenicity study.

The repeat dose toxicity study was of 4 weeks duration in rats using SC doses of up to 7 times the clinical dose. The toxicity was mainly seen in the reproductive system and was consistent with the pharmacology of FSH and LH.

There were two local tolerance studies on rabbits using multiple IM or SC injections of 600 IU or 1200 IU – they appeared to be well tolerated. Single dose studies using 75 IU were also unremarkable.

The evaluator was of the opinion that the absence of allergenicity studies was acceptable, provided that the potential for hypersensitivity was addressed in the clinical data.

The evaluator recommended approval on nonclinical grounds.

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<sup>18</sup> EMEA, Committee for Proprietary Medicinal Products (CPMP), 14 February 1996. Note for Guidance on Virus Validation Studies: the Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses, CPMP/BWP/268/95.

<sup>19</sup> EMEA, Committee for Proprietary Medicinal Products (CPMP), October 1997. ICH Topic Q 5 A (R1). Note for Guidance on Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Derived from Cell Lines of Human or Animal Origin, CPMP/ICH/295/95.

## Clinical

### Pharmacodynamics

The evaluator commented on the balance of FSH and LH activity in Menopur (which is stated to be 1:1), the extent of LH activity contributed by hCG and the source of hCG. It was noted that the original clinical evaluation report stated that menopausal gonadotrophin preparations typically contain FSH and LH preparations in a ratio of 1:1 and some LH activity is derived from added hCG. The evidence presented shows a high proportion of hCG in Menopur (hCG: LH = 20:1). Differentiation of these hormones can only be made by immune reactivity as biological activity is similar.

### Pharmacokinetics

Study **CS 05** was a bioequivalence study which reported the results of the specified primary outcome parameters,  $AUC_{0-144}$  and  $C_{max}$  for baseline corrected FSH (Table 2).

In relation to  $C_{max}$  and AUC, the two formulations met the established criteria of bioequivalence with the 90% CI being within the bounds of 0.80 and 1.25. The evaluator noted that the failure of AUC to cross unity may indicate the possibility of approximately 5% of subjects experiencing a significant difference in drug exposure. The evaluator was of the opinion that it was not important in clinical practice. Other derived pharmacokinetic parameters for FSH were similar between the two formulations.

The evaluator was of the opinion that the two formulations were qualitatively and quantitatively similar.

The evaluator concluded that there is an appropriate rise in FSH after the use of single and multidose formulations proposed for registration. LH activity could not be confirmed, partly due to technical failure of the assays. SC administration was comparable to IM administration and appears more effective in relation to some parameters. Minor changes in formulation appeared to affect pharmacokinetics; however, this may not have clinical consequence as the PI recommends individual titration.

The Delegate noted that the sponsor's claim in the letter of application about menotrophins having different pharmacodynamic effects (compared with preparations with FSH activity alone) has not been verified with formal pharmacodynamic studies in humans. Since the LH activity could not be measured accurately (due to assay problems), it is not possible to dispute the assertions of the protein chemistry evaluator about the potential for longer duration of action. Thus, the raised issue remains a concern.

The submission, as a new chemical entity, is deficient in this respect: there are no studies to systematically characterise the pharmacokinetics and pharmacodynamics of FSH and LH versus Australian registered recombinant products. This is a significant deficiency.

### Efficacy

One of the efficacy studies of this application (**MFK/IVF/0399E**) has been submitted before and discussed in the previous clinical evaluation report. This was a multicentre, randomised parallel group comparator, Phase III study of Menopur vs Gonal-f in women undergoing IVF/ICSI programs. This was a noninferiority study where the primary outcome variable was the rate of ongoing pregnancies (defined as foetal heart rate 10 weeks after oocyte retrieval). Ongoing pregnancy rate was 23.3% for the Menopur group and 20.6% for the Gonal-f group with the two sided 95% CI being -3.3%, 8.7%, thus, confirming noninferiority. The secondary efficacy outcomes also showed noninferiority.

A sub-analysis by fertilisation method (IVF or ICSI) showed that there were higher pregnancy rates in the IVF group. However, the evaluator recommended cautious interpretation due to relatively small numbers and borderline levels of significance.

Study **CS003** was a randomised, open label, single blind, parallel group, multicentre study comparing Menopur vs Gonal-f (rFSH). This was a superiority study in women undergoing IVF. The primary objective was to establish superiority of Menopur compared to Gonal-f with respect to ongoing pregnancy in the study population.

Though there was a trend towards superiority this was not statistically significant. The statistics were switched to noninferiority, the margins preset in the protocol as stipulated in the TGA-adopted EU guideline. The evaluator noted that the lower bound of the 95% CI was well above the pre-specified noninferiority limit of 0.65. PP analysis yielded similar results. The evaluator questioned the selection of the margin of 0.65; however was satisfied with the sponsor's response and concluded that the findings support noninferiority.

The evaluator stated that "There was no difference in LH concentrations between the treatment groups, consistent with the failure to demonstrate LH by immunoassay in subjects receiving Menopur in pharmacokinetic study CS05". The evaluator noted that the subjects who received Menopur required higher overall doses and a longer duration of treatment. The relevance of this was unclear.

**CS 002** was also a randomised open label (investigator blinded) parallel group, multicentre study to establish non inferiority of Menopur vs Gonal-f in women with anovulatory infertility who failed clomiphene treatment. The primary efficacy parameter was ovulation rate. The selected margin of noninferiority was 20%, thus to establish noninferiority the lower margin of the difference between treatment would be greater than -20%. The result in the PP set was 0.17 (-11.0, -11.33). Similar results were found in the ITT population. The evaluator noted that the proportion of subjects achieving biochemical, clinical and ongoing pregnancy were closely similar between the treatment groups. Other secondary outcomes (various indices of follicular development and endometrial thickening) showed no statistical difference between groups. The evaluator noted that as in the previous study, there was a longer duration of treatment and higher total dosage in the Menopur group.

An integrated efficacy analysis of the two Phase III RCT studies (MFK/IVF/0399E and CS003) comparing Menopur with rFSH was presented. The evaluator accepted this analysis as valid as the two studies were very similar in terms of patient selection and clinical protocol. The principle efficacy outcome was live birth resulting from treatment. The results show a significant treatment effect in favour of Menopur.

### ***Overall efficacy conclusions***

There was evidence of noninferiority to other rFSH regimens for COH. Superiority was not seen in study CS 003; however the integrated analyses suggest a trend towards superiority. In relation to ovulation induction, there was noninferiority seen.

### **Safety**

The evaluator noted that the incidence of OHSS was similar between the two treatment groups. The incidence was in line with those reported in IVF and ICSI cycles.

### **Overall recommendation of the evaluator**

Overall, a recommendation to approve the products for requested indications was made. The lack of studies for the male indication was considered to be overcome with published data.

## **Risk Management Plan**

The Office of Product Review recommended routine pharmacovigilance and risk minimisation activities.

## **Risk-Benefit Analysis**

### **Delegate Considerations**

The following issues were considered significant.

#### ***Characterisation***

Standardisation of Menopur has not been fully established as the glycosylation profile is not well characterised. The degree of glycosylation affects the potency and duration of response. This has not been verified in pharmacokinetic studies.

#### ***Lack of adequate pharmacodynamic and kinetic data***

There are no studies to systematically characterise the pharmacokinetics and pharmacodynamics of FSH and LH versus Australian registered recombinant products. This is a significant deficiency as this is a new chemical entity and submitted as a stand-alone product, yet has minimum data on pharmacology.

#### ***Efficacy***

##### ***Patient selection***

Overall efficacy has been seen in comparison with Gonal-f in terms of the two pivotal studies submitted. The integrated analysis of the two studies showed “a statistically significant treatment effect of Menopur on a number of outcome parameters including ongoing pregnancy and live birth rate”. The evaluator also stated, with regard to the OI indication, “trial CS002 amply demonstrates noninferiority of Menopur with respect to rFSH and supports this treatment being of equal clinical value to rFSH, with no particular advantage being suggested or claimed”.

The evaluator of the original submission stated that it has been suggested that adequate LH levels contribute to higher oestradiol levels, the selection of rapid development of larger follicles and possibly reduced rates of OHSS. She stated that the results of MFK/IVF/0399E are consistent with the existence “of a sub-population of women who have a requirement for additional LH and do not respond adequately to FSH alone”. Thus in comparing efficacy of Menopur with Gonal-f (containing FSH alone), the sponsor has not addressed the question, who should have Menopur rather than FSH alone? The current data set does not address this and supports the arbitrary administration of additional LH to subjects who may not require this.

Thus, the Delegate was of the opinion that the subject population who would benefit from this product have not been clearly defined. A subject population preselected to FSH response should have been the inclusion criteria, in order rule out the effect of LH contained in Menopur.

##### ***Indications for which data are provided***

Data are provided only for controlled ovarian hyperstimulation and anovulatory infertility. As a stand-alone submission (and not a biosimilar) males with insufficient spermatogenesis have not been studied.

##### ***Off label use***

There may be an inclination to use this product in conditions where LH may be required. However, there are no data submitted to support this.

## **Safety**

### ***Sterility***

Though the viral and prion safety evaluation concludes that there are no outstanding safety issues, the risk of prion transmission is not entirely ruled out as the risk is categorised as being “low”. It should be noted that in this context, the assays used to detect these are insensitive; and there have been reports of prion transmission in urine. This concern is not allayed by the clinical data set which is limited to a total of 878 patients to 75IU and 50 patients to 1200 IU according to the RMP evaluator. This number is inadequate to establish safety in relation to diseases of viral transmission. Larger numbers are required for this. The RMP set up for Australia is a routine one and does not include additional measures to mitigate risk.

### ***RMP***

The sponsor may argue that there are several hundred thousands (450, 000) who have been exposed to this product since 2008. However, postmarket reports are not sufficiently rigorous nor have they been undertaken for a reasonable period of time to allay fears of viral transmission. Unless there is a patient registry where there is a long term (> 10 years) follow up for atypical infections and neurodegenerative conditions, PSURs are not likely to be of clinical relevance in this regard. Patients need to be followed up over a twenty year period, to satisfactorily monitor for these events.

### ***Place in therapy***

Any obvious advantage over registered recombinant products has not been shown in this submission. The pivotal study, CS 003 which was designed as a superiority study (vs recombinant FSH) failed to show superiority and thus only provided evidence of noninferiority.

### ***Stand-alone product***

This is a new chemical entity of a combination product containing FSH and luteinising activity. The rationale for using LH or hCG that contribute to luteinising activity has not been clearly provided. The pharmacokinetics or dynamics of the luteinising component has not been characterised. No rationale is provided for the use LH (or hCG) in the sought after indications. The Delegate agreed with the evaluator that there may be a subpopulation that may benefit from LH activity. However, this has not been defined.

Based on these issues identified, the Delegate proposed to reject this application. Should the advisory committee recommend approval, the following should be noted:

- The clinical data only support, controlled ovarian hyperstimulation to induce the development of multiple follicles for assisted reproductive technologies (ART) (IVF/ET), gamete intrafallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI) and anovulatory infertility, including polycystic ovarian disease (PCOD), in women who have been unresponsive to treatment with clomiphene citrate.
- “LH” component needs to be standardised to satisfaction of PSC.
- A patient registry is essential. All patients need to be followed up for 20 years. Patients should provide informed consent as there is a safer alternative available on the market.
- An RMP should be submitted to the TGA in relation to “off-label” use.

- The sponsor's claim in the letter of application that Menopur will provide a wider choice for individualised treatment- In this context, the rationale for the inclusion of LH (or hGH) should be further explored, with confirmatory Phase III studies in indications where LH will be of benefit. These will address the issue of unapproved use.

### **Response from Sponsor**

Addressing each of the Delegate's reasons for rejection, the sponsor's views in summary were as follows:

#### ***Characterisation***

The active ingredient in Menopur complies with the BP. It is a unique mixture of isoforms of FSH, LH and hCG which has been well characterised (including its glycosylation profile) and its batch to batch consistency has been demonstrated.

#### ***Lack of adequate PD and PK data***

The pharmacokinetics of FSH and luteinising components (LH and hCG) have been characterised and the pharmacodynamics following Menopur have been well studied including in comparison to the current treatment, rFSH.

#### ***Efficacy***

Menopur has been demonstrated to be noninferior to rFSH in terms of efficacy and safety in the indications of COH and anovulatory infertility. The target population has been clearly identified and Menopur should be available as an alternative treatment option to rFSH for COH and anovulatory infertility on the basis of demonstrating at least equivalent efficacy and safety in these indications. The sponsor agreed to withdraw the application for the male indication. The risk for off label use is minimal and the Administrative Appeals Tribunal has recognised this is not a valid reason for rejection.

#### ***Safety***

TSE risk has been evaluated according to the TGA guidelines and found to be satisfactory by the viral safety evaluator.

#### ***Place in therapy***

The clinical data submitted show noninferiority in COH and anovulatory infertility compared to rFSH which is the mainstay of current treatment. The sponsor maintained that "place in therapy" is not a valid reason for rejection as there is no requirement in the Therapeutic Goods Act to establish a level of efficacy of the drug beyond the purpose for which it is to be used (proposed indication) and it is unlawful to reject a product because it is not more efficacious than another.

#### ***Stand-alone product***

The rationale for the combination of FSH and LH activity in Menopur has been outlined. In short, the two cell theory of gonadotrophins suggests that although only FSH is required for early folliculogenesis, full ovarian steroidogenesis is dependent on LH activity. The clinical data support the use of Menopur in the indications of anovulatory infertility and COH for which registration is sought.

#### **Advisory Committee Considerations**

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended rejection of the submission.

In making this recommendation, the ACPM considered that there was inadequate quality, safety and efficacy data submitted. The characterisation of the product was no better than that submitted in 2004 and was insufficient to quantify the active ingredients of a complex human derived product. The Committee advised that the risk benefit profile was not acceptable because of the uncharacterised inherent batch to batch variation in activity. This meant that the efficacy and safety of different batches could not be predicted based on the results of the submitted clinical studies. The ACPM advised that the added LH in hCG was redundant for the vast majority of patients and may even be detrimental for some by causing inappropriate luteinisation. It is only in hypogonadal women where their LH concentrations are <1 in the presence of amenorrhoea that LH is required. In addition, it was also noted that the LH component of this product was not fully characterised.

The safety data submitted on the limited number of subjects enrolled in clinical trials was inadequate to rule out disease caused by viral and/or prion transmission or uncommon but significant allergic or other immunologically mediated adverse reactions.

### **Initial Outcome**

Based on a review of quality, safety and efficacy, TGA rejected the registration of Menopur (gonadotrophin-human menopausal) 600 IU and 1200 IU powder and solvent solution for injection for the indications of:

- Anovulatory infertility, 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 intrafallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI).

It was noted that during the evaluation phase for this current application, the sponsor withdrew the application for the 75 IU vial and also the indication, "in males, insufficient spermatogenesis caused by hypogonadotropic hypogonadism".

### **Final Outcome**

Following the initial decision described above, the sponsor appealed under Section 60 of the Therapeutic Goods Act whereby a review of the initial decision was conducted by the Minister.

The Delegate of the Minister noted that the Act requires (s25) that the Secretary must evaluate the goods for registration having regard to (amongst other things):

"whether the quality, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established."

The Delegate of the Minister evaluated these three aspects of the application.

### **Quality**

The Delegate of the Minister was satisfied that the product is prepared by fractionation procedures and ion exchange chromatography. The process used to produce the product involves the discarding of some fractions that contain high LH (as measured by immunoactivity) and the concentration of hCG (as measured by immunoactivity). The pooling of various sub-fractions results in the production of a product with a ratio of IU of LH activity to IU of FSH activity of approximately 1.

A consequence of the method of manufacture of the product is that the ratio of LH activity to FSH activity is achieved without the need for hCG derived from the urine of pregnant women to be added. The addition of hCG from the urine of pregnant women is a permitted



but not obligatory requirement of the production section of the monograph for Menotrophin, British Pharmacopoeia 2011 (BP).

The Delegate of the Minister noted that concern has been expressed by the quality evaluator that the product does not comply with the monograph. While the Delegate of the Minister was of the view that the product complies with the BP monograph as written, he was not certain that the BP Commission had in mind the use of a method of production similar to or identical with the sponsor's method of manufacture when the monograph was prepared. The Delegate of the Minister also noted that the monograph for Menotropins in the United States' Pharmacopeia states that: "When necessary, Chorionic Gonadotropin obtained from the urine of pregnant women may be added to achieve this ratio. Not more than 30 percent of the luteinizing hormone activity is contributed by Chorionic Gonadotropin, as determined by a validated method." The Delegate of the Minister noted that, separately to this decision, he would recommend to the National Manager, TGA, that the matters of the permitted source and permitted content of hCG be referred to the BP Commission for review and clarification.

The Delegate of the Minister noted that another consequence of the method of manufacture of the product is that it contains a high proportion of hCG compared with LH. The sponsor agreed in correspondence with the TGA that hCG has a considerably longer half-life than LH. The extent to which hCG in the product continues to exist in the circulation and continues to have LH activity is not measured by the biological assay method for LH activity in the BP monograph.

The Delegate of the Minister was of the view that it is likely that the product will have an extended period of LH activity when compared with other urinary derived products complying with the BP monograph or when doses of LH derived from recombinant technology with presumed equal LH activity are given along with FSH. This fact deserves to be known by doctors administering the product and can be achieved by the inclusion in the Product Information (PI) of a statement under Precautions.

Further to these matters, the Delegate of the Minister noted it was important that the unique method of manufacture of the product reliably produces a consistent product. The Delegate of the Minister was of the view that there is a need for the sponsor to demonstrate batch to batch consistency of product proposed for distribution in Australia. To meet that need, a condition requiring prior submission of batch samples and assay results for a number of batches was required.

### **Efficacy**

The Delegate of the Minister took into account the clinical evaluation report and the view of the Advisory Committee on Prescription Medicines (ACPM). Both the report and the Committee concluded that efficacy has been demonstrated. The Delegate of the Minister noted that the Integrated Analysis comparing Menopur with rFSH showed a statistically significant effect in favour of Menopur (Odds Ratio 1.36 (95% CI: 1.01;1.83; p=0.041).

### **Safety**

The Delegate of the Minister noted that there is a legitimate concern that the use of a product derived from human urine may expose healthy women to the risk of transmission of viral or prion associated diseases. That possibility is supported in Independent Expert Statement which was included in the sponsor's appeal documentation.

The Delegate of the Minister noted that the advice of the TGA's evaluator was that there is not thought to be a risk with product derived from the urine of women in Argentina. The Delegate of the Minister also noted that the issue of the safety of urinary derived fertility hormones has been questioned in a relatively recent publication from Canada. The

Delegate of the Minister understood that the TGA has not received a formal view of the Canadian publication from the National Health and Medical Research Council's TSE Advisory Committee.

The Delegate of the Minister was of the view that information about the possibility of transmission should be included in the PI under Precautions and that this possibility should also be conveyed clearly in the Consumer Medicines Information (CMI).

The Delegate of the Minister noted that there is at least one other product on the Australian market derived from human urine. The Delegate of the Minister noted that, separately to this decision, he will recommend to the National Manager, TGA that a formal opinion of the NHMRC TSE Advisory Committee be obtained with respect to the safety of products derived from human urine and the relevance of the recent Canadian publication.

The Delegate of the Minister was of the view that the chance of Menopur transmitting a viral or prion associated disease was sufficiently low as to not justify a requirement that the sponsor put in place a dedicated registry of patients. The Delegate of the Minister believed that should a patient treated with Menopur subsequently, in the relatively distant future, develop such a disease it is likely that the fertility treatment will be recalled and that records will be able to be accessed. The Delegate of the Minister noted also that, although details provided by the Independent Expert were sparse, there is an established ANZARD registry for subjects of assisted reproductive technology.

The Delegate of the Minister ascertained that the possible detriment from "inappropriate luteinisation" mentioned in the ACPM minutes was intended as a reference to premature luteinisation. The Delegate of the Minister understood from the further advice of the member of ACPM that this is a contentious issue. It was understood from the advice of the member of ACPM and from the report of the Independent Expert that with the use of GnRH analogues, and particularly GnRH antagonists, in COS for ART that this should not occur. Based on that advice, the Delegate of the Minister formed the view that concern about premature luteinisation is not a ground for refusing registration and, further, is known to those clinicians involved in this procedure and is not a matter that warrants a warning statement in the PI.

The Delegate of the Minister also noted the concern of the initial Delegate that the clinical data set is limited. In the view of the Delegate of the Minister, this places insufficient weight on the postmarketing experience as summarised in the clinical evaluation report.

### **Conclusion**

The Delegate of the Minister found that the sponsor had provided information sufficient to establish the quality, safety and efficacy of the product subject to some specific matters. He therefore decided to revoke the initial decision to refuse to register Menopur and decided that the Menopur brand of gonadotrophin menopausal 600 IU and 1200 IU powder and solvent for injection may be registered on the Australian Register of Therapeutic Goods for the following indication(s):

*Anovulatory infertility, 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 intrafallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI).*

Pursuant to section 28 of the Act, the Delegate of the Minister also decided to impose the following specific conditions on the registration of Menopur:

- The Product Information and the Consumer Medicines Information applying to this therapeutic good must be approved by the Therapeutic Goods Administration before Menopur may be supplied;
- The first matter under Precautions in the Product Information must be as follows:

“The active ingredient of this preparation is extracted of human urine. Therefore the risk of a transmission of a pathogen (known or unknown) cannot be completely excluded.” Similar wording must be included in the Consumer Medicines Information;

- The second matter under Precautions in the Product Information must be as follows:

“The Luteinising Hormone activity of Menopur is almost totally contributed by human Chorionic Gonadotrophin (hCG), which has a longer plasma half-life than Luteinising Hormone. As a consequence, the duration of Luteinising Hormone activity of Menopur may differ from that of recombinant Luteinising Hormone products.”

- At least the first five batches of Menopur imported into Australia are not released for sale until samples of each batch have been tested and approved by the TGA Office of Laboratories and Scientific Services (OLSS) and the manufacturer’s release data have been evaluated and approved by OLSS.

## **Attachment 1. Product Information**

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at [www.tga.gov.au](http://www.tga.gov.au).

## DRAFT AUSTRALIAN PRODUCT INFORMATION

### NAME OF THE MEDICINE

MENOPUR<sup>®</sup> (human menopausal gonadotrophin), powder and solvent for solution for injection

MENOPUR 600 IU (600 IU/mL after reconstitution): Each vial with powder contains highly purified menotrophin (human menopausal gonadotrophin, hMG) corresponding to follicle stimulating hormone activity FSH 600 IU and luteinising hormone activity LH 600 IU.

MENOPUR 1200 IU (600 IU/mL after reconstitution): Each vial with powder contains highly purified menotrophin (human menopausal gonadotrophin, hMG) corresponding to follicle stimulating hormone activity FSH 1200 IU and luteinising hormone activity LH 1200 IU.

Human Chorionic Gonadotrophin (hCG), a naturally occurring hormone in postmenopausal urine, is present in MENOPUR and is the main contributor of the LH activity.

CAS number: 9002-68-0

### DESCRIPTION

Menotrophin (hMG, human Menopausal Gonadotrophin) is described in both the British Pharmacopoeia (BP) and the United States Pharmacopeia (USP). Highly purified hMG drug substance is obtained from the urine of menopausal/postmenopausal women. Highly purified hMG is an almost white or slightly yellow powder containing not less than 2000 IU of FSH and LH activity per mg of substance. It is soluble in water. The three gonadotrophins Luteinising Hormone (LH), human Chorionic Gonadotrophin (hCG) and Follicle-Stimulating Hormone (FSH) have been identified in the drug substance.

Powder and solvent for solution for injection.

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

Appearance of solvent: clear colourless solution.

Excipients:

Powder: Lactose, polysorbate 20, sodium phosphate dibasic, phosphoric acid

Solvent: meta-Cresol, Water for injections.

### PHARMACOLOGY

Pharmacotherapeutic group: Gonadotrophins

ATC code: G03G A02

Human Chorionic Gonadotrophin (hCG), a naturally occurring hormone in postmenopausal urine, is present in MENOPUR and is the main contributor of the LH activity.

Menotrophin, which contains both FSH and LH activity, induces ovarian follicular growth and development as well as gonadal steroid production in women who do not have primary ovarian failure. FSH is the primary driver of follicular recruitment and growth in early folliculogenesis, while LH is important for ovarian steroidogenesis and is involved in the physiological events leading to the development of a competent pre-ovulatory follicle. Follicular growth can be stimulated by FSH in the total absence of LH, but the resulting follicles develop abnormally and are associated with low oestradiol levels and inability to luteinise to a normal ovulatory stimulus.

In line with the action of LH activity in enhancing steroidogenesis, oestradiol levels associated with treatment with MENOPUR are higher than with recombinant FSH preparations in downregulated IVF/ICSI cycles. This issue should be considered when monitoring patients' response based on oestradiol levels. The difference in oestradiol levels is not found when using low-dose ovulation induction protocols in anovulatory patients.

### **Pharmacokinetics**

The pharmacokinetic profile of the FSH in MENOPUR has been documented. After 7 days of repeated dosing with 150 IU MENOPUR in downregulated healthy female volunteers, maximum plasma FSH concentrations (baseline-corrected) (mean  $\pm$  SD) was  $8.9 \pm 3.5$  IU/L for the SC administration. Maximum FSH concentrations were reached within 7 hours. After repeated administration, FSH was eliminated with a half-life (mean  $\pm$  SD) of  $30 \pm 11$  hours for the SC administration. Although the individual LH concentration versus time curves show an increase in the LH concentration after dosing with MENOPUR, the data available were too sparse to be subjected to a pharmacokinetic analysis. In a bioequivalence study (CS05) utilising a single dose of 450 IU of MENOPUR in downregulated healthy female volunteers, serum hCG was below the assay limit of detection at baseline in all subjects, consistent with their non-pregnant pre-menopausal state, and rose following administration of MENOPUR in a time profile similar to that of FSH.

Menotrophin is excreted primarily via the kidneys.

The pharmacokinetics of MENOPUR in patients with renal or hepatic impairment has not been investigated.

## **CLINICAL TRIALS**

### **Anovulatory infertility**

CS002 was a prospective randomised clinical trial in 184 women with WHO Group II anovulatory infertility failing to ovulate or conceive on clomiphene citrate. Ovarian stimulation was achieved using a low-dose step-up protocol. The study was designed to document the non-inferiority of MENOPUR SC versus a recombinant FSH preparation (GONAL-F) SC with respect to ovulation rate after one cycle of gonadotrophin treatment.

MENOPUR was demonstrated to be non-inferior to rFSH with respect to ovulation rate (Table 1). In addition to the PP and ITT analyses yielding identical conclusions, the result of the sensitivity analysis adjusting for age and BMI was consistent,

supporting the robustness of the conclusion drawn from the primary analysis. Significantly fewer intermediate-sized follicles were observed in the MENOPUR group (P<0.05). The singleton live birth rate was comparable between the two groups. The frequency of ovarian hyperstimulation syndrome and/or cancellation due to excessive response was 2.2% with MENOPUR and 9.8% with rFSH (P=0.058).

**Table 1: Efficacy outcomes of anovulation in study CS002 (one cycle of treatment)**

Parameter	PP		ITT	
	MENOPUR SC	rFSH SC	MENOPUR SC	rFSH SC
Ovulation rate (%)	85.7	85.5	83.5	84.9
Lower limit of 95% CI*	-11%		-12%	

\*Pre-specified non-inferiority limit was -20%

### Controlled ovarian hyperstimulation

Study 0399E (European and Israeli Study Group trial, EISG), was a Phase 3, randomised study in 727 infertile females undergoing ovarian stimulation to produce multiple follicles for IVF and embryo transfer (IVF/ET) after pituitary suppression with a GnRH agonist. The study was designed to demonstrate non-inferiority of MENOPUR with respect to a recombinant FSH preparation (GONAL-F). The pre-specified non-inferiority limit was -10%. Randomisation was stratified by insemination technique (conventional IVF vs ICSI). Efficacy was assessed based on the primary efficacy parameter of ongoing pregnancy. The initial daily dose of gonadotrophin was 225 IU SC for 5 days. Thereafter the dose was individualised according to each patient's response, up to a maximum of 450 IU/day for a total maximum duration of stimulation of 20 days. Treatment outcomes are summarised in Table 2. The result confirmed that MENOPUR is non inferior to rFSH with respect to ongoing pregnancy rates. Rates of clinical and biochemical pregnancies were also comparable, as were overall safety results.

**Table 2: Efficacy Outcomes for IVF study 0399E (one cycle of treatment)**

Parameter	MENOPUR SC (n = 373)	rFSH SC (n=354)
Ongoing pregnancy	87 (23.3%)	73 (20.6%)
Clinical pregnancy	98 (26.3%)	78 (22.0%)

CS003 (menotrophin versus recombinant FSH (GONAL-F) in vitro fertilisation trial, MERIT), was a Phase 3, randomised study in 731 women undergoing IVF following downregulation with a GnRH agonist. The study was designed as a superiority study (convertible to non-inferiority with a pre-specified non-inferiority limit of an odds ratio of 0.65) with respect to the primary outcome measure, ongoing pregnancy rate. Randomisation was stratified by age. The starting dose of gonadotrophin was 225 IU SC for the first 5 days. Thereafter the dose could be adjusted individually, according to the subject's follicular response. Treatment outcomes are summarised in the table below. The odds ratio of ongoing pregnancy was 1.25 in favour of MENOPUR (95% CI 0.89-1.75). Non-inferiority of MENOPUR with respect to rFSH was demonstrated (Table 3).

**Table 3: Efficacy Outcomes for IVF study CS003**

Parameter	MENOPUR SC (n = 363)	rFSH SC (n=368)
Ongoing pregnancy	97 (26.7%)	82 (22.3%)
Clinical pregnancy	100 (27.5%)	87 (23.6%)

A retrospective integrated analysis, comprising 986 IVF patients and 472 ICSI patients in these two trials, has been performed. In patients undergoing IVF, the live birth rate per cycle initiated was 25.6% (130/491) with MENOPUR and 20.8% (103/495) with rFSH (P=0.041). The odds ratio in favour of MENOPUR was 1.36 (95% CI: 1.01-1.83). Results for patients undergoing ICSI showed no statistically significant difference in live birth rate between MENOPUR and rFSH.

### INDICATIONS

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

Anovulatory infertility, 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)).

### CONTRAINDICATIONS

Pregnancy and lactation.

Hypersensitivity to the active substance or any of the excipients used in the formulation

MENOPUR is contraindicated in women who have:

- Tumours of the pituitary gland or hypothalamus
- Ovarian, uterine or mammary carcinoma
- 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.

### PRECAUTIONS

The active ingredient in this preparation is extracted from human urine. Therefore, the risk of transmission of a pathogen (known or unknown) cannot be completely excluded.

The luteinising hormone activity of MENOPUR is almost totally contributed by Human Chorionic Gonadotrophin (hCG), which has a longer plasma half-life than Luteinising Hormone. As a consequence, the duration of luteinising hormone activity of MENOPUR may differ from that of recombinant products.

MENOPUR is a potent gonadotrophic 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.

Gonadotrophin therapy requires a certain time commitment by physicians and supportive health professionals, and calls for monitoring of ovarian response with ultrasound, alone or in combination with measurement of serum oestradiol levels, on a regular basis. 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, hyperprolactinaemia 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 administration regimen, 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 following symptoms may be observed in severe cases of OHSS: abdominal pain, 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, ascites, haemoperitoneum, pleural effusions, hydrothorax, acute pulmonary distress, and thromboembolic events.

Excessive ovarian response to gonadotrophin treatment seldom gives rise to OHSS unless hCG is administered to trigger ovulation. Therefore in cases of ovarian hyperstimulation it is prudent to withhold hCG and advise the patient to refrain from coitus or to use barrier 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.

Adherence to recommended MENOPUR dosage, regimen of administration and careful monitoring of therapy will minimise the incidence of ovarian hyperstimulation and multiple pregnancy. In ART, aspiration of all follicles prior to ovulation may reduce the occurrence of hyperstimulation.

OHSS may be more severe and more protracted if pregnancy occurs. Most often, OHSS occurs after hormonal treatment has been discontinued and reaches its maximum severity 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.

Women with polycystic ovarian syndrome (PCOS) are at higher risk of developing OHSS. Other reported risk factors that increase the risk of developing OHSS include previous episodes of OHSS, many follicles and high level of oestradiol.

### **Systemic diseases**

Menotrophin is anticipated to be used in patients who, apart from infertility, are otherwise healthy. The safety of menotrophin in individuals with systemic disease, including renal or hepatic disease, has not been studied and the safety profile in these individuals is unknown. Caution should be used when prescribing menotrophin to individuals with clinically relevant systemic disease.

### **Multiple pregnancy**

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

In patients undergoing ovulation induction with gonadotrophins, the incidence of multiple pregnancies is increased compared with natural conception. The majority of multiple conceptions are twins. To minimise the risk of multiple pregnancy, careful monitoring of ovarian response is recommended.

In patients undergoing ART procedures, the risk of multiple pregnancy is related mainly to the number of embryos replaced, their quality and the 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**

Women with generally recognised risk factors for thromboembolic events, such as personal or family history, severe obesity (Body Mass Index > 30 kg/m<sup>2</sup>) or thrombophilia may have an increased risk of venous or arterial thromboembolic events, during or following treatment with gonadotrophins. 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.

### **Use in pregnancy (Category C)**

MENOPUR is contraindicated in women who are pregnant (see CONTRAINDICATIONS). Although no adequate animal studies have been conducted with MENOPUR, based on its pharmacology and reproductive studies conducted with similar products, an increase in embryonic resorptions and post-implantation loss may be expected at clinically relevant doses.

### **Use in lactation**

MENOPUR should not be used during lactation (see CONTRAINDICATIONS).

### **Paediatric use**

MENOPUR should not be used in children.

### **Use in the elderly**

MENOPUR should not be used in the elderly.

### **Genotoxicity**

The genotoxic potential of MENOPUR has not been investigated. Gonadotrophins are naturally occurring proteins and unlikely to pose a genotoxic risk.

### **Carcinogenicity**

No carcinogenicity studies have been performed in animals.

## **INTERACTIONS WITH OTHER MEDICINES**

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 desensitisation, a higher dose of MENOPUR may be necessary to achieve adequate follicular response.

## ADVERSE EFFECTS

### Clinical Trials

The most frequently reported adverse drug reactions reported during treatment with MENOPUR in clinical trials are abdominal pain, headache, injection site reactions and injection site pain, with an incidence rate up to 10%. Table 4 displays the main adverse drug reactions in women treated with MENOPUR in clinical trials, distributed by system organ classes (SOCs) and frequency.

**Table 4: Adverse Reactions – Clinical Trials**

System Organ Class	Common ( $\geq 1/100$ and $< 1/10$ )
Nervous system disorders	Headache
Gastrointestinal disorders	Abdominal pain, Nausea, Enlarged abdomen
Reproductive system disorders	OHSS, Pelvic pain
General disorders and administration site condition	Injection site reaction, Injection site pain

Gastrointestinal symptoms associated with OHSS such as abdominal distension and discomfort, nausea, vomiting and diarrhoea have been reported with MENOPUR in clinical trials. As rare complications of OHSS, venous thromboembolic events and ovarian torsion might occur.

### Post-marketing Experience

Table 5 displays adverse drug reactions reported in women treated with MENOPUR in the post-marketing period, distributed by system organ classes (SOCs).

**Table 5: Adverse Reactions – Post Marketing**

System Organ Class	Frequency not known*
Immune system disorders	Hypersensitivity**
Nervous system disorders	Dizziness
Eye disorders	Visual disorders***
Skin and subcutaneous tissue disorders	Rash, Pruritus
Musculo-skeletal and connective system disorders	Arthralgia
Reproductive system disorders	Breast tenderness
General disorders and administration site condition	Pyrexia

\* The frequency of adverse drug reactions reported during the post-marketing period is regarded as unknown.

\*\* Allergic reactions localised or generalised, including anaphylactic reaction

\*\*\* Vision disorders such as blurred vision, vision impairment including amaurosis, diplopia, mydriasis, photopsia, scotoma and vitreous floaters have been reported with MENOPUR during the post-marketing period.

## **DOSAGE AND ADMINISTRATION**

Treatment with MENOPUR should be initiated under the supervision of a physician experienced in the treatment of fertility problems.

### **Method of administration**

MENOPUR is intended for subcutaneous (S.C.) injection after reconstitution with the solvent provided.

The powder should be reconstituted prior to use. The reconstituted solution is for multiple injections and can be used for up to 28 days. Each reconstituted MENOPUR 600 IU or 1200 IU vial should be for individual patient use only.

### General

Vigorous shaking should be avoided. The solution should not be used if it contains particles or if it is not clear.

### **Dosage**

There are great inter-individual variations in the response of the ovaries to exogenous gonadotrophins. This makes it impossible to set a uniform dosage scheme. The dosage should, therefore, be adjusted individually depending on the ovarian response.

MENOPUR can be given alone or in combination with a gonadotrophin-releasing hormone (GnRH) agonist or antagonist. Recommendations about dosage and duration of treatment may change depending on the actual treatment protocol.

### **Women with anovulatory infertility (including PCOD)**

The object of MENOPUR therapy is to develop a single Graafian follicle from which the oocyte will be liberated after the administration of human chorionic gonadotrophin (hCG).

MENOPUR therapy should start within the initial 7 days of the menstrual cycle. The recommended initial dose of MENOPUR is 75-150 IU daily, which should be maintained for at least 7 days. Based on clinical monitoring (including ovarian ultrasound alone or in combination with measurement of oestradiol levels) subsequent dosing should be adjusted according to individual patient response. Adjustments in dose should not be made more frequently than every 7 days. The recommended dose increment is 37.5 IU per adjustment, and should not exceed 75 IU. The maximum daily dose should not be higher than 225 IU. If a patient fails to respond adequately after 4 weeks of treatment, that cycle should be abandoned and the patient should recommence treatment at a higher starting dose than in the abandoned cycle.

When an optimal response is obtained, a single injection of 5,000 IU to 10,000 IU hCG should be given 1 day after the last MENOPUR injection. The patient is recommended to have coitus on the day of and the day following hCG administration. Alternatively intrauterine insemination (IUI) may be performed. If an excessive response to MENOPUR is obtained treatment should be stopped and hCG withheld (see PRECAUTIONS) and the patient should use a barrier method of contraception or refrain from having coitus until the next menstrual bleeding has started.

### **Women undergoing controlled ovarian hyperstimulation for multiple follicular development for assisted reproductive technologies (ART)**

In line with clinical trials with MENOPUR that involved downregulation with GnRH agonists, MENOPUR therapy should start approximately 2 weeks after the start of agonist treatment. The recommended initial dose of MENOPUR is 150-225 IU daily for at least the first 5 days of treatment. Based on clinical monitoring (including ovarian ultrasound alone or in combination with measurement of oestradiol levels) subsequent dosing should be adjusted according to individual patient response, and should not exceed more than 150 IU per adjustment. The maximum daily dose given should not be higher than 450 IU daily and in most cases dosing beyond 20 days is not recommended.

In protocols not involving downregulation with GnRH agonists, MENOPUR therapy should start on day 2 or 3 of the menstrual cycle. It is recommended to use the dose ranges and regimen of administration suggested above for protocols with downregulation with GnRH agonists.

When a suitable number of follicles have reached an appropriate size, a single injection of up to 10,000 IU hCG should be administered to induce final follicular maturation in preparation for oocyte retrieval. Patients should be followed closely for at least 2 weeks after hCG administration. If an excessive response to MENOPUR is obtained treatment should be stopped and hCG withheld (see PRECAUTIONS) and the patient should use a barrier method of contraception or refrain from having coitus until the next menstrual bleeding has started.

### **Instructions for use and handling**

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

Attach the reconstitution needle to the pre-filled syringe. Inject the total contents of solvent into the vial containing the powder. MENOPUR 600 IU must be reconstituted with one pre-filled syringe with solvent before use. MENOPUR 1200 IU must be reconstituted with two pre-filled syringes with solvent before use. 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.

The administration syringes are graduated in FSH/LH units from 37.5 - 600 IU and supplied with needles in the MENOPUR multidose box. Draw up the reconstituted solution from the vial into the administration syringe for injection according to the prescribed dose. Each mL of reconstituted solution contains 600 IU FSH and LH.

Draw up the exact dose of reconstituted solution from the vial into the syringe for injection and administer the dose immediately.

### **General**

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.

### **OVERDOSAGE**

The effects of an overdose are unknown, nevertheless one could expect ovarian hyperstimulation syndrome to occur.

## **PRESENTATION AND STORAGE CONDITIONS**

MENOPUR is available in the following containers and pack sizes:

### MENOPUR 600 IU

Powder: 2 mL colourless glass (Type I glass) vial with rubber stopper closed with a cap.

Solvent: 1 mL pre-filled syringe (Type I glass) with rubber tip cap and plunger, rubber stopper.

The 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.

### MENOPUR 1200 IU

Powder: 2 mL colourless glass (Type I glass) vial with rubber stopper closed with a cap.

Solvent: 1 mL pre-filled syringe (Type I glass) with rubber tip cap and plunger, rubber stopper.

The 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.

### **Storage conditions**

Store in a refrigerator (2°C to 8°C). Do not freeze. Store in the original container. To reduce microbiological hazard, the reconstituted solution should be stored in a refrigerator and must be discarded after 28 days. Chemical and in-use stability have been demonstrated for reconstituted product stored for up to 28 days at not more than 25°C.

## **NAME AND ADDRESS OF THE SPONSOR**

Ferring Pharmaceuticals Pty Ltd  
Suite 2, Level 1, Building 1, 20 Bridge Street  
Pymble NSW 2073

## **POISON SCHEDULE OF THE MEDICINE**

Prescription Medicine

## **Date of first inclusion in the Australian Register of Therapeutic Goods (ARTG)**

XXXXXX

## **Date of most recent amendment**

N/A

## **Therapeutic Goods Administration**

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Reference/Publication #