PUBLIC SUMMARY DOCUMENT
Product: HUMAN MENOPAUSAL GONADOTROPHIN, powder for injection, 600 IU and 1200 IU with solvent, Menopur®
Sponsor: Ferring Pharmaceuticals Pty Ltd
Date of PBAC Consideration: March 2012

1. Purpose of Application

The submission sought a Section 100 (IVF/GIFT Program) listing for a patient who is receiving medical treatment as described in items 13200, 13201, 13202 or 13203 of the Medicare Benefits Schedule.

2. Background

This presentation of human menopausal gonadotrophin (hMG) had not previously been considered by the PBAC.

Various brands and presentations of hMG have been listed on the PBS for the treatment of anovulatory infertility since 1988. The last available presentation of hMG was deleted from the PBS on 1 February 2004.

3. Registration Status

Human menopausal gonadotrophin (Menopur®) was TGA registered on 13 September 2011 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).

4. Listing Requested and PBAC's View

Section 100 (IVF/GIFT Program)
Criteria for availability
Patients who are receiving medical treatment as described in items 13200, 13201, 13202 or 13203 of the Medicare Benefits Schedule.

Note
Supply of these items is through an accredited IVF/GIFT clinic.

For PBAC's view, see Recommendations and Reasons.

5. Clinical Place for the Proposed Therapy

Controlled ovarian hyperstimulation, as part of assisted reproductive technologies (ART), involves administration of injectable gonadotrophins to sustain high FSH concentrations, thus prompting the development of multiple mature follicles in the ovaries. FSH (either recombinant (rFSH) or urinary-derived (uFSH) and hMG are commonly used treatments internationally. Currently in Australia, rFSH is the only available treatment option.

The submission proposed the place in therapy for hMG (which contains three gonadotrophins – LH, human chorionic gonadotrophin (hCG) and FSH) is as an alternative gonadotrophin preparation to the current rFSH products available on the PBS.

6. Comparator

The submission nominated follitropin alfa (GONAL-f®) as the comparator. This comparator was accepted by the PBAC.

7. Clinical Trials

The submission presented six randomised trials comparing hMG with follitropin alfa (EISG 2002, Kilani 2003, Andersen 2006, Bosch 2008, Hompes 2008 and CS004) in patients undertaking assisted reproductive technologies (ART) (in vitro fertilisation/embryo transfer (IVF/ET), gamete intra-fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)). The submission also presented a meta-analysis of all six randomised trials and an integrated analysis of two trials (EISG 2002 and Andersen 2006). Details of the trials published at the time of submission are in the table below.

Trial ID/First author	Protocol title/ Publication title	Publication citation
Direct randomised trial(s)		
EISG 2002 EISG. European and Israeli Study Group on Highly Purified Menotropin versus recombinant FSH	Efficacy and safety of highly purified menotropin versus recombinant follicle stimulating hormone in in vitro fertilization/intracytoplasmic sperm injection cycles: a randomized, comparative trial	Fertil Steril, 2002; 78, No. 3, p520–28.
Helmgaard L et al	Children born after controlled ovarian stimulation with HP-hMG or recombinant FSH: results of the EISG pregnancy outcome follow-up	Abstract no. P-272 ASRM, Philadelphia 2004
Platteau P et al	Does exogenous LH activity influence the outcome in IVF and not in ICSI cycles?	Fertil-Steril (80, Suppl. 3, S105, 2003)
Platteau P et al	Exogenous luteinizing hormone activity may influence the treatment outcome in in vitro fertilization but not in intracytoplasmic sperm injection cycles.	Fertility and sterility, Vol. 81, No. 5, p. 1401-4, May 2004
Kilani 2003 Kilani Z et al	A prospective, randomized, controlled trial comparing highly purified hMG with recombinant FSH in women undergoing ICSI: ovarian response and clinical outcomes.	Human Reproduction 18, No. 6, p1194–1199. 2003
Kilani Z et al	Elevated efficacy of highly purified human menopausal gonadotropin (HP hMG) for intracytoplasmic sperm injection (ICSI): results of a prospective, randomized, controlled trial comparing HP hMG to recombinant follicle-stimulating hormone (r-FSH).	Fertil-Steril (76, No. 3, Suppl., S53, 2002)

Andersen 2006 Andersen A N, et al, for the MERIT Group	Clinical outcome following stimulation with highly purified hMG or recombinant FSH in patients undergoing IVF: a randomized assessor-blind controlled trial	Hum Reprod, Vol 21, No.12 pp3217–27, 2006;
Pettersson-Goeran et al	Pre-stimulation parameters predicting live birth after IVF in the long GnRH agonist protocol.	Reproductive BioMedicine Online, {Reprod-BioMed-Online}, May 2010, vol. 20, no. 5, p. 572-581,
Andersen AN et al	Comparing highly purified hMG and rFSH in patients undergoing IVF - Reply.	Human Reproduction, 2007, V22, N6, JUN, pp 1798-1800.
Ziebe S et al	Influence of ovarian stimulation with HP-hMG or recombinant FSH on embryo quality parameters in patients undergoing IVF.	Human Reproduction (Oxford England), {Hum-Reprod}, Sep 2007 (epub: 19 Jul 2007), vol. 22, no. 9, p. 2404-13
Smitz J et al	Endocrine profile in serum and follicular fluid differs after ovarian stimulation with HP-hMG or recombinant FSH in IVF patients.	Human Reproduction (Oxford England), {Hum-Reprod}, Mar 2007 (epub: 16 Nov 2006), vol. 22, no. 3, p. 676-87
Arce J C et al	Interobserver agreement and intraobserver reproducibility of embryo quality assessments.	Human Reproduction, {Hum-Reprod}, August 2006, vol. 21, no. 8, p. 2141-2148
Bosch 2008	Highly purified hMG versus recombinant FSH in ovarian hyperstimulation with GnRH antagonists--a randomized study.	Hum Reprod. Vol 23, No.10 pp2346-51, 2008
Hompes 2008	Effectiveness of highly purified human menopausal gonadotropin vs. recombinant follicle-stimulating hormone in first-cycle in vitro fertilization-intracytoplasmic sperm injection patients.	Fertil Steril. Vol 89, No.6, p1685-93, 2008
CS004 Strowitzki T	By treatment protocols – differences in treatment outcomes after downregulation 2007 (Interim analysis)	5th World Congress on Ovulation Induction. Rome, Italy, September 13-15, 2007

Integrated analysis of trials EISG 2002 and Andersen 2006		
Platteau P et al	Highly purified HMG versus recombinant FSH for ovarian stimulation in IVF cycles.	Reproductive Biomedicine Online, {Reprod-Biomed-Online}, Aug 2008, vol. 17, no. 2, p. 192-200
Sorensen P et al	Live birth rate in IVF cycles is significantly higher after stimulation with highly purified menotrophin compared with recombinant FSH.	Human Reproduction (Oxford), Jun 2006, vol. 21, no. Suppl. 1, p. I124-I125,
Arce JC et al	A pooled analysis of two large randomized trials comparing ongoing pregnancy rates with highly purified menotropin and recombinant FSH in IVF cycles.	Fertility-And-Sterility, 2005, V84, SEP, S1, p S320
Hirrle-Baerbel	In vitro fertilization (IVF): Optimized ovarian stimulation - Significantly higher live births following stimulation with highly purified hMG. (In-vitro-Fertilisation (IVF): Optimierte ovarielle stimulation - Signifikant mehr lebendgeburten nach therapie mit HP-hMG.)	Gynakologie,{Gynakologie}, 2006, vol. 11, no. 5, p. 33-35

8. Results of Trials

The key outcomes presented in the submission were ongoing pregnancy rate and live birth rate.

Meta-analysis

For the results of the meta-analysis for ongoing pregnancy rate, the PBAC noted that there was no significant difference between hMG or follitropin alfa for the risk ratio, point estimate of effect (95% CI; p-value), 1.12 (0.98, 1.28; p=0.10) or the risk difference 0.03 (-0.01, 0.06; p=0.10). There was no indication of heterogeneity between the trials ($I^2 = 0\%$) and the confidence intervals were narrow.

Data on live births were available for all six trials. However, as the study by Hompes 2008 reported cumulative live birth rate including 1-year outcome of cryopreserved cycles, it was excluded from the analyses. For the results for live births, the PBAC noted that there was no significant difference between hMG or follitropin alfa for the risk ratio, point estimate of effect (95% CI; p-value), 1.14 (0.98, 1.34; p=0.10) and for the risk difference 0.03 (-0.01, 0.07) (p=0.10). There was no indication of heterogeneity between the trials ($I^2 = 0\%$) and the point estimates slightly favoured hMG.

Integrated analysis

The results of the integrated analysis of the EISG 2002 and Andersen 2006 trials for Ongoing Pregnancy rate and Live Birth Rate are summarised in the table below

Integrated analysis EISG 2002/Andersen 2006

Ongoing pregnancy rate after one cycle				
	MENOPUR n/N (%)	**Gonal-f n/N (%)**	**MENOPUR vs Gonal-f Odds ratio [95% CI]**	**P-value**
IVF	134/491 (27.3%)	105/495 (21.2%)	1.38 [1.03 ; 1.86]	0.030
ICSI	50/245 (20.4%)	50/227 (22.0%)	0.90 [0.58 ; 1.40]	0.630
Live Birth				
IVF	130/491 (26.5%)	103/495 (20.8%)	1.36 [1.01 ; 1.83]	0.041
ICSI	46/245 (18.8%)	46/227 (20.3%)	0.89 [0.56 ; 1.41]	0.630

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.

There was no statistically significant difference between hMG and follitropin alfa with respect to ongoing pregnancy and live birth in patients undergoing ISCI (p=0.6.30). For patients undergoing IVF, there was a statistically significant difference favouring hMG for both ongoing pregnancy and live birth rates.

The PBAC noted that based on the outcomes from all six trials the safety profiles of hMG and follitropin alfa appeared to be similar. No significant differences were reported for adverse events, serious adverse events, multiple births, pregnancy loss or neonatal health. One trial, Hompes 2008, reported a statistically significant difference in ovarian hyperresponse and/or OHSS in favour of hMG.

The PBAC noted that the TGA has requested that the following statement be included in the PI for Menopur, because hMG is derived from human urine:

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

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission described hMG as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over follitropin alfa. The PBAC accepted the submission's claim. *See Recommendation and Reasons.*

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses were estimated as hMG 1.01 IU and follitropin alfa 1.00 IU (total average dose 2,386 IU hMG and 2,350 IU follitropin alfa) based on a weighted average dose estimate from the key trials.

The PBAC considered that there were significant uncertainties associated with the equi-effective dose calculation due to substantial variation in individual patient response to gonadotrophins. However, based on the available information the equi-effective doses were considered reasonable.

11. Estimated PBS Usage and Financial Implications

The submission did not present any information on the likely number of patients treated. The submission stated that increased costs of hMG would be offset by reduction in costs of

substituted drugs (follitropin alfa and follitropin beta), and estimated that the financial impact of listing hMG would be $0 in all years.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC recommended the listing of human menopausal gonadotrophin (hMG), powder for injection, 600 I.U. and 1,200 I.U. under the Section 100 IVF/ GIFT Program for patients who are receiving medical treatment as described in items 13200, 13201, 13202 or 13203 of the Medicare Benefits Schedule on a cost minimisation basis with follitropin alfa. The equi-effective doses are hMG 1.01 I.U. and follitropin alfa 1.00 I.U., based on the weighted average dose estimate from the key trials; EISG 2002, Kilani 2003, Andersen 2006, Bosch 2008, Hompes 2008 and CS004 2009. The PBAC noted that the listing should result in no net financial cost to the PBS.

In making this recommendation the PBAC considered there would be additional wastage with the use of hMG in comparison to follitropin alfa in the order of 150 I.U. per patient (across the dose range), considering the submission's supposition that hMG will substitute for follitropin alfa on a unit for unit basis. The PBAC noted that the average dose supplied per cycle for follitropin alfa and follitropin beta was estimated in the Pre-Sub-Committee Response (and Pre-PBAC Response) to be 3,600 IU. This is considerably higher than the weighted average doses in the clinical trials (2,386 IU hMG and 2,350 IU follitropin alfa). The PBAC considered that there may be considerable wastage with these products in clinical practice. The PBAC also noted the availability of different strengths of follitropin alfa (300 I.U., 450 I.U. and 900 I.U. multi dose cartridge) compared to those of hMG (600 I.U. and 1,200 I.U. powder for injection). The PBAC noted that any difference in dose regimen, the number of packs used or wastage may result in either an additional cost to the PBS (if more IU of hMG is needed compared to follitropin alfa) or a cost saving (if more IU of follitropin alfa is needed compared to hMG). The PBAC therefore considered that the price of hMG should factor in a percentage wastage for drug loss related to the mode of administration and vial strengths.

The PBAC considered that hMG is of non-inferior efficacy to follitropin alfa in terms of ongoing pregnancy and live birth rate based on the evidence presented in the submission.

The PBAC noted the consumer comments on this item, including a concern about the risk of pathogen transmission based on the derivation of hMG from human urine. The PBAC noted that human chorionic gonadotrophin is also derived from human urine and is currently listed on the IVF/GIFT Program. The PBAC also referred to comments provided by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) noting that gonadotrophin products derived from human urine have been used worldwide for many years without any reports of infectious disease being transmitted from them, including prion disorders. Noting these considerations and based on the safety data presented in the submission, the PBAC accepted that hMG is of non-inferior safety to follitropin alfa. The PBAC noted that hMG will offer an additional clinical option in IVF treatment.

Recommendation:
HUMAN MENOPAUSAL GONADOTROPHIN, powder for injection, 600 units and 1,200 units, with solvent.

Restriction:	Section 100 (IVF/GIFT Program) Criteria for availability Patients who are receiving medical treatment as described in items 13200, 13201, 13202 or 13203 of the Medicare Benefits Schedule. Note Supply of these items is through an accredited IVF/GIFT clinic. For enquiries relating to the IVF/GIFT Program, medical practitioners should contact Medicare Australia on 1800 700 270.
Pack size:	1

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Ferring welcomes the PBAC decision to recommend listing of human menopausal gonadotriphin (Menopur®) for use in the IVF/GIFT Program.