

7.15 HIGHLY PURIFIED HUMAN MENOPAUSAL GONADOTROPHIN, powder for injection, 600 I.U, Menopur[®], Ferring Pharmaceuticals Pty Ltd.

1 Purpose of Application

1.1 The minor resubmission sought to address the issues outlined by the PBAC in their rejection of the major submission at the March 2016 meeting for highly purified human menopausal gonadotropin (HP-hMG) for anovulatory infertility.

2 Requested listing

2.1 The resubmission requested the following listing:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
GONADOTROPHIN gonadotrophin-menopausal human international units injection [1 x 600 international units vial] & inert substance diluent [1 x 1mL syringes], 1 pack	600 3	0	\$ [REDACTED]*	Menopur® Ferring

Category / Program	GENERAL – General Schedule (GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Anovulatory infertility
PBS Indication:	Anovulatory infertility
Restriction Level / Method:	<input checked="" type="checkbox"/> Restricted benefit
Administrative Advice	<p>Except in cases of hypopituitarism or primary amenorrhoea, the patient should have been adequately treated with clomiphene citrate and/or gonadorelin and failed to have conceived.</p> <p>Women who have had apparent ovulation induced by other agents and have failed to conceive should have laparoscopic evidence that there is no other impediment to conception.</p> <p>Oligomenorrhoea should have been present for at least twelve months or amenorrhoea for at least six months prior to treatment.</p> <p>Patients with hyperprolactinaemia should have had appropriate surgical or medical treatment prior to treatment.</p>

* The pre-PBAC response noted that since the minor resubmission there has been a reduction in the price of the comparator follitropin alfa. The pre-PBAC response updated the requested DPMQ to \$ [REDACTED] (or \$ [REDACTED] with a maximum quantity of 4).

3 Background

- 3.1 HP-hMG was TGA registered in July 2011 for women with anovulatory infertility, and controlled ovarian hyperstimulation as part of an Assisted Reproductive Technology (ART) treatment program.
- 3.2 In March 2012, the PBAC recommended listing HP-hMG as an Authority required item under Section 100 (IVF program) for use as part of ART. Listing was on a cost-minimisation basis against follitropin alfa. The equi-effective doses were 1.01 IU of HP-hMG and 1 IU follitropin alfa. For the ART indication HP-hMG was listed at a lower price per IU compared with follitropin alfa to reflect the dose relativity of 1.01:1 and additional wastage. Specifically, HP-hMG was listed with an AEMP per IU that was 7.8% lower than for follitropin alfa.
- 3.3 Two gonadotrophins are currently listed under Section 85 for patients with anovulatory infertility, follitropin alfa and follitropin beta. The PBAC has previously accepted that follitropin beta is equivalent to follitropin alfa on a per unit basis (therapeutic relativity sheets – 1 December 2016).
- 3.4 The PBAC rejected HP-hMG in March 2016 for the treatment of anovulatory infertility (gonadotrophin public summary document (PSD), March 2016 PBAC meeting). The PBAC considered that extending the listing of HP-hMG would not address any unmet clinical need. The evidence presented in the March 2016 submission did not adequately support a claim of non-inferiority to the comparator, follitropin alfa, and the PBAC considered that there was considerable uncertainty regarding the equi-effective doses.
- 3.5 A summary of the previous submission, the PBAC’s view, and the current resubmission is provided in Table 1.

Table 1: PBAC issues in previous submission and how the current resubmission addresses them

PBAC Issues	Sponsors claim March 2016 Submission	PBAC view March 2016 Submission	Current resubmission November 2016
Clinical need	<ul style="list-style-type: none"> The sponsor argued that there is a strong rationale for the listing of a gonadotrophin containing LH activity for anovulatory infertility. The sponsor claimed that HP-hMG contains FSH activity and LH activity in a 1:1 ratio, unlike follitropin alfa which only contains FSH activity and possesses different pharmacodynamics effects. 	<ul style="list-style-type: none"> The PBAC decided not to recommend extending the listing of HP-hMG as this would not address any unmet clinical need for anovulatory infertility. 	<ul style="list-style-type: none"> The resubmission disagreed with the PBAC comments and again argued that there is a strong rationale for the listing of a gonadotrophin containing LH activity for anovulatory infertility. The resubmission provided evidence in the form of statements from clinicians supporting the clinical need for HP-hMG for treatment of anovulatory infertility.

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PBAC Issues	Sponsors claim March 2016 Submission	PBAC view March 2016 Submission	Current resubmission November 2016
Clinical claim: Non-inferiority	<ul style="list-style-type: none"> The sponsor described HP-hMG as non-inferior in terms of comparative effectiveness and comparative safety over follitropin alfa. The sponsor claimed that the non-inferiority margin of 20% for the ovulation rate is clinically acceptable as this had been used in a previous clinical trial CS2002. 	<ul style="list-style-type: none"> The PBAC considered that the evidence presented in the submission did not adequately support a claim of non-inferiority. The PBAC noted that the non-inferiority margin of -20% was met for the primary outcome of ovulation rate, although considered the CI around the main difference to be wide (-1.43% [95% CI: -12.0, 9.1]). The PBAC noted that for the patient relevant outcome of live births and ongoing pregnancy, the lower confidence interval exceeded the 10% non-inferiority margin previously accepted by the PBAC. 	<ul style="list-style-type: none"> The resubmission provided no new clinical data and argued that a high quality randomised trial (CS2002) has demonstrated non-inferiority of efficacy in comparison to follitropin alfa.
Equi-effective dose	<ul style="list-style-type: none"> 1 IU of HP-hMG and 1 IU of follitropin alfa over a treatment cycle based on CS002. 	<ul style="list-style-type: none"> The PBAC considered that there was considerable uncertainty regarding the equi-effective doses. The evaluator and ESC advised different equi-effective dose ratios (1.46:1 [mean ITT] and 1.32:1 [median ITT], respectively). 	<ul style="list-style-type: none"> 1.14 IU of HP-hMG and 1 IU of follitropin alfa based on the ratio of median doses from the per protocol population.
Wastage and financial issues	<ul style="list-style-type: none"> The sponsor claimed that the majority of substitution of HP-hMG for the currently supplied gonadotrophin products is expected for 900IU and that there is no difference in the quantity supplied per script. Therefore, indicating there is no expected change in wastage. The sponsor claimed that should a total dose of 1200IU be prescribed, clinicians can prescribe 2 packs in place of 2 packs of Puregon 600IU, where wastage would be identical. 	<ul style="list-style-type: none"> The PBAC noted that the proportion of patients requiring a second prescription was likely to be higher with HP-hMG compared to follitropin alfa due to the potential requirement for higher doses. The PBAC noted that there was potential for more wastage as HP-hMG is only available in one strength, while follitropin alfa is available in three strengths. 	<ul style="list-style-type: none"> The sponsor claims cost savings based on a comparison of the DPMQ for HP-hMG versus follitropin alfa. The resubmission requested that if PBAC remains of the opinion that the equi-effective dose ratio should be the median of the ITT population rather than the median of the PP population, the maximum quantity should be increased to 4 to ensure sufficient drug per script for a cycle and to avoid a second prescription.
Outcome		<ul style="list-style-type: none"> Submission rejected. The 	<ul style="list-style-type: none"> No new data provided.

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PBAC Issues	Sponsors claim March 2016 Submission	PBAC view March 2016 Submission	Current resubmission November 2016
		PBAC advised that should the sponsor wish to make a resubmission (in the absence of new data), the sponsor could propose a claim of inferior comparative effectiveness to follitropin alfa.	<ul style="list-style-type: none"> The clinical claim is unchanged from the March 2016 submission.

Source: gonadotrophin PSD, March 2016 PBAC meeting; and minor resubmission.

For more detail on PBAC's view, see section 7 "PBAC outcome".

4 Clinical place for the proposed therapy

- 4.1 Gonadotrophins are used as a second-line treatment for ovulation induction in women who do not ovulate or conceive on clomiphene citrate. Follitropin alfa and follitropin beta are follicle stimulating hormones (FSH) and are used to assist follicular growth and ovulation.
- 4.2 HP-hMG, which contains both FSH and luteinising hormone (LH) activity, induces ovarian follicular growth and development as well as gonadal steroid production in women who do not have primary ovarian failure and is proposed as an alternative gonadotrophin. The clinical place was unchanged compared with the March 2016 submission.
- 4.3 In March 2016, the PBAC considered that extending the listing of HP-hMG would not address any unmet clinical need for anovulatory infertility. The minor resubmission presented statements from clinicians addressing the need for a gonadotrophin containing LH for anovulatory infertility and specifically the need for women with low LH levels. The minor resubmission claimed that HP-hMG was associated with the development of fewer follicles, which would lead to more single live births and reduced risk of interrupted cycles due to excessive ovarian response or risk of ovarian hyperstimulation syndrome.

5 Comparator

- 5.1 The major submission considered by the PBAC in March 2016 nominated follitropin alfa as the main comparator. This was considered appropriate by the PBAC. The comparator was unchanged in the minor resubmission.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item as it was a minor submission.

Consumer comments

6.2 The PBAC noted and welcomed the input from one health care professional via the Consumer Comments facility on the PBS website. The comment indicated that patients with low levels of LH benefit from the combination of FSH and LH activity through HP-hMG for ovulation induction. The comment also noted the anomaly that patients are able to access subsidised HP-hMG if they proceed to IVF treatment.

Clinical trials

6.3 As a minor resubmission, no new clinical trials were presented. The minor resubmission represented the following clinical trial from the March 2016 major submission.

Table 2: Trial and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
CS002	<p>FE999906 CS002</p> <p>A Randomized, Open-label, Assessor-blind, Parallel Group, Multi-Center, Non-inferiority Study Comparing Highly Purified Menotrophin (MENOPUR) SC and Recombinant FSH (GONAL-F) SC for Ovulation Induction Using a Chronic Low-dose Step-up Protocol in Women with WHO Group II Anovulatory Infertility Failing to Ovulate or Conceive on Clomiphene Citrate</p> <p>Platteau P. Similar ovulation rates, but different follicular development with highly purified menotrophin compared with recombinant FSH in WHO Group II anovulatory infertility: a randomised controlled study.</p> <p>Arce JC & Smitz J: Exogenous hCG activity, but not endogenous LH activity, is positively associated with live birth rates in anovulatory infertility.</p> <p>Platteau P. Ovulation rate with a highly purified menotrophin and a recombinant FSH in women unresponsive to clomiphene citrate.</p>	<p>Ferring Pharmaceuticals. Internal study report. 23 Feb 2005</p> <p>Human Reproduction. 2006; 21 (7): 1798-1804</p> <p>Human Fertility. 2011; 14(3): 192-199.</p> <p>Fertility and Sterility. 2005; 84 (Suppl 1): S324-325.</p>

Source: Table B-3 p 18 of the submission (March 2016 submission)

Comparative effectiveness

6.4 The trial results remain unchanged from the previous major submission considered in March 2016 (see Tables 3 and 4). The March 2016 submission proposed a non-inferiority margin of -20% for ovulation rate. The minor resubmission noted this margin was agreed by regulatory authorities internationally. The PBAC previously considered the confidence interval around the mean difference in ovulation rate to be wide (-1.43% (95% CI: -12.0, 9.1)).

Table 3: Results of the primary outcome (ovulation rate) across the direct randomised trial

	HP-hMG n with event/N (%)	Follitropin alfa n with event/N (%)	Mean difference (95% CI)*
PP	60/70 (85.7)	71/83 (85.5)	0.17 (-11.0, 11.33)
ITT	76/91 (83.5)	79/93 (84.9)	-1.43 (-12.0, 9.10)

Source: Table B-17, Table B-18 p48, of the March 2016 submission; CS002 CSR Table 9-1 p73, Table 9-9 p81.

Abbreviations: CI = confidence interval; HP-hMG = highly purified human menopausal gonadotrophin; ITT = intention-to-treat; PP = per protocol.

* Pre-specified non-inferiority limit = -20%

Table 4: Results of the patient-relevant secondary outcomes across the direct randomised trial

	HP-hMG n with event/N (%)	Follitropin alfa n with event/N (%)	Mean difference (95% CI)*
Ongoing pregnancy (PP)	13/70 (18.6)	14/83 (16.9)	1.70% (-10.5%, 13.9%)
Ongoing pregnancy (ITT)	13/91 (14.3)	16/93 (17.2)	-2.92% (-13.4%, 7.59%)
Live births (ITT)	13/91 (14.3)	16/93 (17.2) ^a	-2.92% (-13.4%, 7.59%)

Source: Table B-19 p50, text p51 of the March 2016 submission; CS002 CSR Table 9-1 p73, Table 9-9 p81.

Abbreviations: CI = confidence interval; HP-hMG = highly purified human menopausal gonadotrophin; ITT = intention-to-treat; PP = per protocol.

^a The CSR report Table 11-3 p116 there were 18 live-born children in the follitropin alfa group. Two subjects in the trial had multiple pregnancies which resulted in twins. There were no twin pregnancies in the HP-hMG group.

* The March 2016 submission did not nominate a non-inferiority limit for ongoing pregnancy (PP or ITT). The PBAC previously accepted a 10% margin.

- 6.5 In March 2016, the PBAC noted that all ongoing pregnancies in both treatment arms resulted in live births. The mean difference in the proportion of patients with a live birth for HP-hMG and follitropin alfa was 2.92% (95% CI: -13.4%, 7.59%). The March 2016 major submission did not nominate a non-inferiority margin for the outcomes of live births or ongoing pregnancy. However, in March 2016 the PBAC noted that it had previously accepted a -10% non-inferiority margin for live births and ongoing pregnancy (progesterone PSD, March 2014 PBAC meeting) and that this was exceeded by the lower 95% confidence limit.
- 6.6 The pre-PBAC response (p1) stated that the resubmission provided a high quality randomised trial that demonstrated non-inferiority of efficacy in comparison to follitropin alfa. The pre-PBAC response (p1-2) also stated that there are qualitative benefits in favour of HP-hMG related to differential follicular development that compensate for the fact that the lower limit of the 95% confidence interval is slightly below the -10% limit and requested that the PBAC adopt a pragmatic approach in the interpretation of the secondary outcome results of the pivotal study.

Clinical claim

- 6.7 The resubmission claimed non-inferior comparative effectiveness and non-inferior comparative safety of HP-hMG compared with follitropin alfa. In March 2016, the PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data, and that a claim of non-inferior safety of HP-hMG to follitropin alfa may be reasonable.
- 6.8 The PBAC considered that the submission did not provide any new data or information to address the issues raised by the PBAC at the March 2016 meeting; the PBAC's previous consideration regarding the clinical claim therefore remained unchanged.

Economic analysis

- 6.9 The equi-effective doses were estimated in the March 2016 submission as 1 IU of HP-hMG and 1 IU of follitropin alfa. In March 2016, the PBAC considered that there was considerable uncertainty regarding the equi-effective doses, noting that the evaluation and the ESC advised different equi-effective dose ratios (1.46:1 and 1.32:1 respectively) to the major submission's proposed 1:1 ratio.
- 6.10 The minor resubmission expressed concern about using a dose ratio from the clinical trial as it claimed that imbalances in the baseline characteristics of the study population may have contributed to a higher mean dose of HP-hMG compared to follitropin alfa. The submission further stated the clinical trial allowed treatment for up to 6 weeks, whereas the TGA-approved Product Information (PI) for HP-hMG only recommends up to 4 weeks of use before abandoning a cycle, and the maximum recommended dose in the PI is 225 IU whereas higher doses were allowed in the trial. The minor resubmission stated that most of the patients who failed to respond adequately after 4 weeks of treatment in the study, where treatment for up to 6 weeks was allowed, did not ovulate and none got pregnant. The resubmission therefore considered the trend towards a longer duration of treatment and resulting high HP-hMG dose, compared with follitropin alfa, observed in the trial is less likely to be seen in Australian clinical practice.
- 6.11 A summary of the dosing data from Study CS002 is presented in Table 5.

Table 5: Summary statistics of total gonadotrophin dose

Summary statistic	Total HP-hMG dose (IU)	Total rFSH dose (IU)	Ratio (HP-hMG:rFSH)
Mean ITT	1491	1022	1.46
Median ITT	1088	825	1.32
Mean PP	1390	981	1.42
Median PP	938	825	1.14

Source: HP-hMG PBAC PSD, March 2016, Table 7

Abbreviations: HP-hMG = highly purified human menopausal gonadotrophin; ITT = intention-to-treat; IU = international units; PP = per protocol, rFSH = recombinant follicle stimulating hormone.

- 6.12 The minor resubmission stated that if an equi-effective dose ratio from the trial is used, it should be the ratio of the median doses from the per protocol population (1.14).
- 6.13 The minor resubmission requested that if PBAC insists on the equi-effective dose ratio of 1.32 and wastage of 7.8%, as proposed by ESC, the maximum quantity should be increased to 4 (2,400 IU) to ensure an appropriate quantity of HP-hMG per script. The pre-PBAC response reiterated this request, stating that based on the 1.32 ratio, the proportion of patients requiring a second script of HP-hMG at a maximum quantity of 4 should be no different to follitropin alfa at a maximum quantity of 3.

Estimated PBS usage & financial implications

- 6.14 Revised financial forecasts were not provided in the minor resubmission.
- 6.15 In March 2016, the PBAC noted that the proportion of patients requiring a second prescription was likely to be higher with HP-hMG compared with follitropin alfa. The

sponsor maintained that the vast majority of patients would be treated with a maximum quantity of 1800 IU (one prescription). The sponsor stated that if the PBAC determined the equi-effective dose ratio to be 1.32, the maximum quantity for HP-hMG could be increased to 2400 IU (4 vials) and this would reduce the need for a second prescription for HP-hMG.

- 6.16 The minor resubmission estimated cost savings per patient per cycle with the use of HP-hMG compared with follitropin alfa:
- \$ [REDACTED] for a HP-hMG price calculated using a dose ratio of 1.14 and a maximum quantity per prescription of 1800 IU; and
 - \$ [REDACTED] for a dose ratio of 1.32 and a maximum quantity of 2400 IU.
- 6.17 The calculated cost saving for the first scenario is based on a patient receiving one prescription of either HP-hMG or follitropin alfa for the maximum quantity (equivalent to 1800 IU) each cycle regardless of the total dose required. Study CS002 indicates that patients require a higher dose of HP-hMG. In March 2016, the PBAC noted that the proportion of patients requiring a second prescription was likely to be higher with HP-hMG compared with follitropin alfa due to the potential requirement for higher doses (paragraph 7.7, PSD, March 2016 PBAC meeting). It was further noted that there was potential for more wastage as HP-hMG is only available in one strength while follitropin alfa is available in three strengths. The calculated cost saving for the second scenario is based on a patient receiving one prescription of either HP-hMG (2400 IU) or follitropin alfa (1800 IU) each cycle regardless of the total dose required. This potentially accounts for the higher dose of HP-hMG required but may result in additional wastage with HP-hMG. Overall, the cost savings presented in the minor resubmission are unlikely to be realised in clinical practice.
- 6.18 Three strengths are available for follitropin alfa, whereas only one strength of HP-hMG is available, which may mean the wastage with follitropin alfa is less than with HP-hMG. The pre-PBAC response (p2-3) stated that the reduction in price of 7.8% has already been applied to account for this possibility, as agreed for the Section 100 (IVF program) listing. In addition, the pre-PBAC response stated that the vast majority of scripts for follitropin alfa are for the 900IU presentation.

For more detail on PBAC's view, see section 7 "PBAC outcome".

7 PBAC Outcome

- 7.1 The PBAC decided not to recommend the PBS listing of HP-hMG for the treatment of anovulatory infertility on the basis that the minor resubmission did not adequately support a claim of non-inferiority to follitropin alfa.
- 7.2 The PBAC recalled that in March 2016 it rejected a major submission for HP-hMG on the basis that the evidence presented did not adequately support a claim of non-inferiority to the comparator, follitropin alfa. The PBAC considered that as no new clinical trial data had been provided in the resubmission, there was an insufficient basis on which to change its previous consideration regarding the claim of non-inferiority to follitropin alfa.

- 7.3 The PBAC further recalled that in March 2016 it considered that extending the listing of HP-hMG would not address any unmet clinical need. On the basis of the clinician statements presented in the minor resubmission, the PBAC considered that there was some evidence of a clinical need for HP-hMG for anovulatory infertility in a small number of women with low levels of LH.
- 7.4 The PBAC noted that reliable equi-effective doses could not be estimated from the CS002 trial as the trial did not adequately demonstrate non-inferiority of HP-hMG and follitropin alfa. Notwithstanding this, the PBAC considered the equi-effective dose ratio proposed in the minor resubmission of 1:1.14 was not adequately supported as it was based on the analysis of the per-protocol population. Based on the analysis of the intention-to-treat population the equi-effective dose ratio was noted to be higher (1:1.32 to 1:1.46).
- 7.5 The PBAC did not accept the sponsor's request for an increase in maximum quantity to 2400 IU on the basis of the requirement for a higher IU dose with HP-hMG compared with follitropin alfa. The PBAC considered that, on balance, the maximum quantity of 1800 IU was more appropriate to minimise wastage, as patients will be able to access a second script if required.
- 7.6 The PBAC considered that the resubmission did not adequately address the issues outlined in the March 2016 submission. The PBAC reiterated its advice from March 2016 that, should the sponsor wish to make a resubmission in the absence of new clinical data, the sponsor could propose a claim of inferior comparative effectiveness to follitropin alfa and provide appropriately adjusted estimates of cost-effectiveness.
- 7.7 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 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.

9 Sponsor's Comment

Ferring is disappointed with this PBAC decision however we will continue to work with physicians, patients and the PBAC to find a way to make ovulation induction with MENOPUR available on the PBS as a treatment option for patients with anovulatory infertility.