

7.07 FOLLITROPIN ALFA and LUTROPIN ALFA injection, 150 IU and 75 IU, Powder for injection, Vial of solvent, 1mL water for injection; Pergoveris[®], Merck Serono Australia Pty Ltd

1 Purpose of Application

- 1.1 The minor re-submission sought listing on the Section 100 (IVF/GIFT) Program, for follitropin alfa and lutropin alfa (Pergoveris[®]), a fixed dose combination (FDC) product of recombinant follicle-stimulating hormone (rFSH) and recombinant luteinising hormone (rLH).
- 1.2 The submission proposes that Pergoveris will be used in the subgroup of patients taking rFSH and rLH concomitantly for whom the fixed dose combination is appropriate.
- 1.3 The current minor re-submission for Pergoveris[®] was reviewed together with the major application for lutropin alfa (Luveris[®]), a rLH, at the March 2015 meeting of the PBAC. Luveris was recommended by PBAC and if it became available on the PBS, those patients for whom the fixed dose combination is not considered appropriate could be treated with the individual components or the dose of Luveris could be titrated.

2 Requested listing

- 2.1 The submission proposes no new changes to the proposed listing.

Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

| | |
|-----------------------------|--|
| Category / Program | Section 100 – IVF/GIFT Treatment |
| 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: | Stimulation of follicular development |
| PBS Indication: | Stimulation of follicular development |
| Restriction Level / Method: | <input checked="" type="checkbox"/> Restricted benefit (criteria for availability) <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined |
| Clinical criteria: | <i>Patient must have severe LH deficiency</i> <i>AND</i> <i>Patient must be receiving medical treatment as described in items 13200, 13201, 13202 or 13203 of the Medicare Benefits Schedule</i> |

| | |
|-----------------------|--|
| Administrative Advice | 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 |
|-----------------------|--|

- 2.2 The submission proposed the listing for Pergoveris[®] a FDC product to be costed as the sum of its components. It is estimated to result in no additional cost to the PBS over the first five years compared to the reimbursed use of its components, Gonal-f (rFSH) and Luveris (rLH).

3 Background

- 3.1 Pergoveris was registered with the Therapeutic Goods Administration (TGA) in 2009 for *“the stimulation of follicular development in women with severe LH and FSH deficiency. In clinical trials these patients were defined by an endogenous serum LH of less than 1.2 IU/L”*.
- 3.2 At the March 2012 meeting, the PBAC rejected a minor submission to list Pergoveris[®]. The PBAC noted that no evidence was presented in the submission that could be used to determine the comparative effectiveness of the combination product and follitropin alfa. Additionally, inadequate evidence was provided of the efficacy of the combination product in the defined sub-group of patients with severe LH and FSH deficiency. At the time, the PBAC considered that these issues would need to be addressed in a major submission to allow full evaluation of the clinical data. The PBAC therefore rejected the submission on the basis of inadequate clinical evidence of comparative effectiveness.
- 3.3 At the March 2014 meeting, the PBAC rejected the major re-submission for the reimbursement of the combination product Pergoveris[®]. The PBAC considered that the absence of rLH in a single-component product was a concern, noting that it would complicate dose titration in clinical practice. The PBAC noted that the submission had not established the comparative effectiveness and safety of the fixed dose combination to either follitropin alfa given alone or the components - follitropin alfa and lutropin alfa given separately or other products containing human menopausal gonadotropin. The PBAC noted that the submission did not present a formal cost-minimisation analysis, and considered that an appropriate cost-minimisation would need to compare follitropin alfa +lutropin alfa FDC with the components administered concomitantly.

See March 2014 PBAC meeting minutes, agenda item 7.5, ‘PBAC Outcome’ for further detail.

4 Clinical place for the proposed therapy

- 4.1 The proposed listing for Pergoveris® FDC product is for the subgroup of women for whom both rFSH regimen with rLH are required to replace a severe deficiency in endogenous LH, and in whom treatment with the FDC product is appropriate. These women represent approximately █% of Assisted Reproductive Technology (ART) cycles, according to the minor re-submission.

5 Comparator

- 5.1 The minor re-submission nominated its two components: follitropin alfa (Gonal-f) and lutropin alfa (Luveris) as comparators. At the March 2014 meeting, the PBAC considered that the comparator should include both FSH and LH rather than follitropin alfa alone.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from health care professionals (12) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with Pergoveris including affordable access to more options in IVF treatment and less risk of dosing errors with the combination product than using two drugs separately, improving compliance and reducing anxiety.
- 6.3 The PBAC noted the advice received from ACCESS Australia's National Infertility Network Ltd clarifying the likely use of Pergoveris in clinical practice. The PBAC specifically noted the advice that the use of Pergoveris may provide the possibility of achieving a pregnancy for a small group of women who have inadequate levels of LH and that some women in this small group for whom LH support is necessary, may in addition require a combination of FSH hormone and Luveris. The PBAC noted that this advice was supportive of the evidence provided in the submission.
- 6.4 No new clinical data are presented for Pergoveris beyond the data presented in the previous submission for Pergoveris and in the current major submission for the listing of Luveris (see agenda item 5.15 of the March 2015 PBAC meeting).

Comparative effectiveness

- 6.5 At the March 2014 meeting, the PBAC considered that the submission had not established the comparative effectiveness and safety of the FDC product to either of its components – follitropin alfa and lutropin alfa.
- 6.6 In March 2014, the PBAC did not consider that the evidence provided for the surrogate endpoint of follicular stimulation was adequate. This minor re-submission refers to the results of the Lehert 2014 meta-analysis presented in the major

submission for Luperis to provide more patient relevant outcomes such as pregnancy and OHSS. The results of the meta-analysis are summarised below.

Summary of the efficacy and safety results of the meta-analysis

| Outcome | Normal responder population | | | Poor Responder population | | |
|-------------------------|--|-------|-------------------------|---------------------------|-------|---------------------------|
| | # | n | | # | n | |
| Clinical pregnancy rate | 29 | 5,214 | RR 1.09 [0.95, 1.24] | 14 | 1,179 | RR 1.30 [1.01, 1.67] |
| Ongoing pregnancy rate | 18 | 5,194 | RR 1.13 [1.00, 1.27] | 11 | 1,043 | RR 1.36 [1.04, 1.79] |
| Live birth rate | 18 | 5,194 | RR 1.10 [0.94, 1.29] | 11 | 1,043 | RR 1.30 [0.95, 1.78] |
| OHSS | 0.61 [0.32, 1.13] in overall population, trend maintained in poor responders | | | | | |
| Total dose of rFSH | 26 | 4,484 | MD -60 [-0.16, 0.04] | 8 | 549 | MD -380 [-0.59, -0.17] |

= number of trials n = number of participants; RR = Risk Ratio; [] represent 95% confidence intervals; MD = Mean difference

Source: Table 4 of minor re-submission, p21

- 6.7 This re-submission included the bioequivalence studies previously provided to PBAC in the March 2014 submission. Study IMP23718 compared the rFSH component to the fixed rFSH/rLH combination, whilst Study IMP23722 compared the rLH component to the fixed combination. The re-submission quoted the AUSPAR (January 2010) conclusion “*The test product “Pergoveris” containing follitropin alfa and lutropin alfa is bioequivalent to the two reference products Gonal-F and Luperis containing the single entity follitropin alfa and lutropin alfa, respectively*” (p23 of the minor re-submission).
- 6.8 The re-submission identified a precedent for accepting bioequivalence evidence as the basis for listing of a combination product on the PBS: the alogliptin and metformin fixed dose combination tablets considered at the November 2013 PBAC meeting.

Comparative harms

- 6.9 The submission presented the results from the Lehert (2014) meta-analysis to address PBAC’s concerns (March 2014) about the comparative safety of the FDC product, particularly the risk of ovarian hyperstimulation syndrome (OHSS) (see Table 1 above).
- 6.10 The submission noted the Lehert (2014) meta-analysis demonstrated that the supplementation with rLH resulted in no increase in the incidence of OHSS.

Clinical claim

- 6.11 The clinical claim for supplementation of the rFSH regimen with rLH compared to no supplementation with rLH is superior efficacy and superior safety. These conclusions are based on the Lehert (2014) meta-analysis and are addressed in the major submission for Luperis.
- 6.12 The minor re-submission proposed that a demonstration of the efficacy and safety of the combination product based on the bioequivalence of the combination and its

components was considered acceptable by the PBAC for alogliptin and metformin and should likewise be acceptable for Pergoveris. The minor re-submission suggested four points should be noted from this precedent:

- The efficacy and safety of the individual components had previously been demonstrated.
- A demonstration of the efficacy and safety of the combination product based on the bioequivalence of the combination and its components was considered acceptable by the PBAC.
- No additional clinical trials in the relevant patient population were presented.
- It was not considered necessary for the bioequivalence studies to include the exact doses of the components present in the combination product. “Data was presented for bioequivalence for the 12.5 mg alogliptin/500 mg metformin and 12.5 mg alogliptin/1000 mg metformin FDC, but was not provided for the 12.5 mg alogliptin/850 mg metformin FDC tablet.” (November 2013 PSD, p3).

6.13 The PBAC considered that the claim of superior comparative effectiveness when compared to the follitropin or compared to lutropin was reasonable for clinical pregnancy but less certain for live birth.

6.14 The PBAC considered that the claim of superior comparative safety was not adequately supported by the data; however it was noted that there was no increase in OHSS in the overall population.

Economic analysis

6.15 The submission proposed that the price for the FDC product is equal to the sum of the prices of its individual components, Luveris (rLH) and Gonal-f (rFSH). The proposed price for rLH component as presented in the Luveris application was \$ [REDACTED] for 75IU. The ex-manufacturer price for the smallest unit size of Gonal-f on the IVF/GIFT program is \$ [REDACTED] for 300IU. The dose of rFSH present in Pergoveris is 150IU, proportionally valued at \$ [REDACTED].

6.16 The proposed price for the FDC product is the sum of its components at the relevant doses is \$ [REDACTED].

Drug cost/patient/cycle: approximately \$ [REDACTED]. This compares to \$ [REDACTED] for women receiving separate rLH and rFSH.

6.17 Pergoveris cycle calculation:

| | |
|---|---------------|
| [REDACTED] packs of Pergoveris ([REDACTED]*\$ [REDACTED]) | \$ [REDACTED] |
| [REDACTED] packs of Gonal-f ([REDACTED]*\$ [REDACTED]) | \$ [REDACTED] |
| Total | \$ [REDACTED] |

6.18 Luveris and Gonal-f as individual components, cycle calculation:

| | |
|--|---------------|
| [REDACTED] packs of Luveris ([REDACTED]*\$ [REDACTED]) | \$ [REDACTED] |
| [REDACTED] packs of Gonal-f ([REDACTED]*\$ [REDACTED]) | \$ [REDACTED] |
| Total | \$ [REDACTED] |

Estimated PBS usage & financial implications

- 6.19 Estimates in the minor re-submission for Pergoveris were based on those presented for the major submission for Luveris. The minor re-submission estimated no additional cost to the PBS over the first five years of listing of Pergoveris compared to the reimbursed use of its components, Gonal-f and Luveris.
- 6.20 The submission proposed that the estimated number of women treated with FDC product is less than 10,000 in Year 1, rising to less than 10,000 in Year 5. The submission proposed that since the listing of Pergoveris on the PBS would be cost-neutral per treatment cycle, the absolute uptake rates and the number of treatment cycles are of minimal significance.
- 6.21 The cost of treatment with Pergoveris is offset by the cost of Luveris no longer required for rLH supplementation and also by the four fewer packs of Gonal-f required to supply the full requirement of rFSH per treatment cycle. The listing of Pergoveris on the PBS will result in minor savings to the PBS of less than \$10 million per year in Year 1, rising to less than \$10 million per year in Year 5 as shown in table below.

Estimated use and financial implications

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|--|---------------|---------------|---------------|---------------|---------------|
| Total cost of Pergoveris | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| Net cost to Government for the drug (a) | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| Net cost to Government from decrease in use of other drugs | | | | | |
| Total cost savings for rFSH no longer required | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| Total cost savings for rLH no longer required | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| TOTAL Savings (b) | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| TOTAL SAVINGS (a-b) | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |

Source: Table 8 of the minor re-submission, p30

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of the fixed dose combination product follitropin alfa and lutropin alfa, on the basis that it should be available only under special arrangements under Section 100 (IVF/GIFT program) listing.
- 7.2 The PBAC recommended the listing on a cost minimisation basis to the individual components.
- 7.3 The PBAC noted the proposed PBS restriction as amended by the Secretariat and considered an additional clinical criteria requiring patients to have been titrated to the FSH and LH doses in the combination product after at least one cycle of treatment would be the best way to ensure use of Pergoveris was restricted to patients for whom treatment with the combination product was considered appropriate.
- 7.4 The PBAC accepted the two components: follitropin alfa (Gonal-f) and lutropin alfa (Luveris) as appropriate comparators.

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- 7.5 As for the major submission for Luveris (agenda item 5.15 at this same meeting), the PBAC accepted, for the poor responder population in the Leherter 2014 meta-analysis, that there were statistically significantly greater numbers of clinical pregnancies in the lutropin alfa + rFSH treatment arm compared to the rFSH only treatment arm.
- 7.6 As for the major submission for Luveris (agenda item 5.15 at this same meeting), the PBAC did not accept the superior safety claim but recognised that OHSS is not a concern with this treatment.
- 7.7 The PBAC considered the proposed estimates of use were acceptable.
- 7.8 The PBAC advised that Pergoveris is not suitable for prescribing by nurse practitioners.
- 7.9 The PBAC recommended that the Safety Net 20 Day Rule should not apply as this is a section 100 item.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

| | |
|-----------------------------|---|
| Category / Program | Section 100 – IVF/GIFT Treatment |
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| Condition: | Stimulation of follicular development |
| PBS Indication: | Stimulation of follicular development |
| Restriction Level / Method: | <input checked="" type="checkbox"/> Restricted benefit (criteria for availability) <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined |
| Clinical criteria: | <i>Patient must have severe LH deficiency</i> <i>AND</i> <i>Patient must be considered appropriate for treatment with the combination product after titration of FSH and LH after at least one cycle of treatment.</i> <i>AND</i> <i>Patient must be receiving medical treatment as described in items 13200, 13201, 13202 or 13203 of the Medicare Benefits Schedule</i> |
| Administrative Advice | <i>Supply of these items is through an accredited IVF/GIFT clinic.</i> <i>For enquiries relating to the IVF/GIFT program, medical practitioners should contact Medicare Australia on 1800 700 270</i> |

9 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.

10 Sponsor's Comment

We note that the Secretariat Overview of our minor submissions confirms "The criteria for availability are consistent with the TGA registered indication." We also note that the PBS supply arrangements for IVF medicines (and therefore Pergoveris) will change as of 1 July 2015, and thus the maximum quantity stated above is incorrect.

Reimbursement of Pergoveris provides an important medicine for some women who may otherwise not achieve a pregnancy. Providing Gonal F and Luveris in a fixed dose combination allows for the reduction in the number of injections women may need. This may reduce dosing errors and improve adherence.