PUBLIC SUMMARY DOCUMENT
Product: Ganirelix, solution for injection, 250 micrograms in 0.5ml (as acetate), single use pre-filled syringe, Orgalutran®
Sponsor: Schering Plough Pty Ltd
Date of PBAC Consideration: November 2009

1. Purpose of Application

The submission sought a Section 100 (IVF/GIFT PROGRAM) listing for the prevention of premature luteinisation and ovulation in patients undergoing controlled ovarian stimulation, followed by oocyte pick-up and assisted reproductive techniques.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Ganirelix was TGA registered on 19 March 2001 for the prevention of premature luteinisation and ovulation in patients undergoing controlled ovarian stimulation, followed by oocyte pick-up and assisted reproductive techniques.

4. Listing Requested and PBAC's View

Section 100 (IVF/GIFT PROGRAM)
For the prevention of premature luteinisation and ovulation in patients undergoing controlled ovarian stimulation, followed by oocyte pick-up and assisted reproductive techniques.

NOTE: Arrangements to prescribe this item should be made by medical practitioners with Medicare Australia, contact telephone number 1800 700 270.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Assisted reproduction manipulates the menstrual cycle of women receiving fertility treatments to maximise the chances of successful ovulation and fertilisation. In women with ovulation disorders, ovulation induction with fertility treatment may be sufficient to achieve conception and pregnancy. For infertility due to tubal damage, male factor infertility and ovulation disorders where ovulation induction alone is not successful, more complex techniques of assisted reproduction may be required. Most require controlled ovarian hyperstimulation (COH) to induce development of several oocytes. Oocytes may then be fertilised within the body, or collected and fertilised outside the body and then the embryo replaced to continue normal development in the uterus.

During controlled ovarian stimulation, follicle stimulating hormone (FSH) is administered to stimulate oocyte development. As soon as the follicles have reached a certain size, an injection of human chorionic gonadotrophin (hCG) or recombinant hCG (r-hCG) is given in place of the body's natural luteinising hormone (LH), which is responsible for triggering ovulation. Oocyte collection has to be precisely timed, as the oocytes must be retrieved before ovulation. Thus, it is important to prevent the surge in natural LH, to prevent premature ovulation and allow the successful oocyte collection. This is done by administration of gonadotropin-releasing hormone (GnRH) analogues, either GnRH agonists or GnRH antagonists.

Ganirelix is a GnRH antagonist and would provide patients with a PBS-subsidised GnRH analogue.

6. Comparator

The submission nominated nafarelin, a GnRH agonist, as the main comparator. The PBAC agreed that this was an appropriate comparator, as nafarelin is the most commonly used GnRH analogue in Australia.

7. Clinical Trials

The submission presented a comparison of GnRH analogues versus non-analogues to establish comparative efficacy and cost-effectiveness of analogues, followed by a comparison of ganirelix versus nafarelin. The submission also presented an indirect comparison of ganirelix versus nafarelin using leuprolide as the common reference.

Analog versus non-analogue stimulation

For the analogue versus non-analogue comparison the submission presented a meta-analysis of 14 randomised trials comparing GnRH analogue stimulation to non-analogue stimulation. None of these trials included ganirelix or nafarelin. Details of the key trials and the meta-analysis are presented in the table below.

Trial ID / First author	Protocol title / Publication title	Publication citation
Direct randomised trials		
Akman et al (2000)	Addition of GnRH antagonist in cycles of poor responders undergoing IVF	Human Reproduction 2000; 15(10): 2145-2147
Akaboshi et al (1998)	The effects of gonadotrophin-releasing hormone agonist on androstenedione production and follicular development during controlled ovarian hyperstimulation.	Journal of Assisted Reproduction and Genetics 1998; 15(8): 478-484
Avrech et al (2004)	Inclusion of standard and low-dose gonadotrophin releasing hormone-analogue (short protocol) in controlled ovarian hyperstimulation regimens in normogonadotropic patients aged 40-48 years who are undergoing in vitro fertilization.	Gynecological Endocrinology 2004; 19(5): 247-252
Neveu et al (1987)	Ovarian stimulation by a combination of a gonadotrophin-releasing hormone agonist and gonadotrophins for in vitro fertilization.	Fertility and Sterility 1987; 47(4): 639-643
Antoine et al (1990)	Ovarian stimulation using human menopausal gonadotrophins with or without LHRH analogues in a long protocol for in vitro fertilization: A prospective randomized comparison.	Human Reproduction 1990; 5(5): 565-569
Kingsland et al (1992)	The routine use of gonadotrophin-releasing hormone agonists for all patients undergoing in vitro fertilization. Is there any medical advantage? A prospective randomized study.	Fertility and Sterility 1992; 57(4): 804-809
Luxman et al (1995)	In vitro fertilization for women with pure tubal occlusion: The impact of short gonadotrophin-releasing hormone agonist treatment.	Fertility and Sterility 1995; 63(2): 357-360
Maroulis et al (1991)	Prospective randomized study of human menotropin versus a follicular and a luteal phase gonadotrophin-releasing hormone analog-human menotropin stimulation protocols for in vitro fertilization.	Fertility and Sterility 1991; 55(6): 1157-1164

Polson et al (1991)	A controlled study of gonadotrophin-releasing hormone agonist (buserelin acetate) for folliculogenesis in routine in vitro fertilization patients.	Fertility and Sterility 1991; 56(3): 509-514
Ron-El et al (1991)	Gonadotrophins and combined gonadotrophin-releasing hormone agonist-gonadotrophins protocols in a randomized prospective study.	Fertility and Sterility 1991; 55(3): 574-578
Van De-Helder et al (1990)	Comparison of ovarian stimulation regimens for in vitro fertilization (IVF) with and without a gonadotrophin-releasing hormone (GnRH) agonist: Results of a randomized study.	Journal of In Vitro Fertilization and Embryo Transfer 1990; 7(6): 358-362
Yang et al (1995)	Comparison of human menopausal gonadotrophin and follicle-stimulating hormone with gonadotrophin-releasing hormone agonist desensitization for controlled ovarian hyperstimulation in in vitro fertilization.	Chinese Medical Journal (Taipei) 1995; 55(6): 452-456
Battaglia et al (1997)	Colour Doppler changes and thromboxane production after ovarian stimulation with gonadotrophin-releasing hormone agonist.	Human Reproduction (Oxford, England) 1997; 12(11): 2477-2482
Gonen et al (1991)	The use of long-acting gonadotrophin-releasing hormone agonist (GnRH-a; decapeptyl) and gonadotrophins versus short-acting GnRH-a (buserelin) and gonadotrophins before and during ovarian stimulation for in vitro fertilization (IVF).	Journal of In Vitro Fertilisation and Embryo Transfer 1991; 8(5): 254-259
Meta-analyses of direct randomised trials		
Hughes et al (1992)	The routine use of gonadotrophin-releasing hormone agonists prior to in vitro fertilisation and gamete intrafallopian transfer: A meta-analysis of randomised controlled trials.	Fertility and Sterility 1992; 58(5): 888-896

Ganirelix versus nafarelin

The comparison of ganirelix and nafarelin was based on one head-to-head trial, with supportive evidence provided by an indirect comparison using leuprolide as the common reference. The key trial is presented in the table below.

Trial ID / First author	Protocol title / Publication title	Publication citation
Rombauts et al (2006)	A comparative randomised trial to assess the impact of oral contraceptive pre-treatment on follicular growth and hormone profiles in GnRH antagonist-treated patients.	Human Reproduction 2006; 21(1): 95-103

Indirect comparison

The indirect comparison of ganirelix versus nafarelin was based on three ganirelix versus leuprolide and three nafarelin versus leuprolide trials. The submission also summarises the results of four published meta-analyses which included a range of antagonists and agonists. Details of the trials included in the indirect comparison and the meta-analyses are presented in the table below.

Trial ID / First author	Protocol title / Publication title	Publication citation
Ganirelix		
Barmat et al (2005)	A randomized prospective trial comparing gonadotrophin-releasing hormone (GnRH) antagonist/recombinant follicle-stimulating hormone (rFSH) versus GnRH-agonist/rFSH in women pretreated	Fertility and Sterility 2005; 83(2): 321-330

	with oral contraceptives before in vitro fertilization.	
Check et al (2004)	Effect of antagonists vs. agonists on in vitro fertilization outcome.	Clinical and Experimental Obstetrics and Gynecology 2004; 31(4):257-259
Fluker et al (2001)	Efficacy and safety of ganirelix acetate versus leuprolide acetate in women undergoing controlled ovarian hyperstimulation.	Fertility and Sterility 2001; 75(1): 38-45
Nafarelin		
Dada et al (1999)	A comparison of three gonadotrophin-releasing hormone analogues in an in vitro fertilization programme: A prospective randomized study.	Human Reproduction 1999; 14(2): 288-293
Dantas et al (1994)	Comparison between nafarelin and leuprolide acetate for in vitro fertilization: Preliminary clinical study.	Fertility and Sterility 1994; 61(4): 705-705
Loh et al (1999)	Nafarelin acetate for pituitary suppressions in in vitro fertilisation cycles – A Singaporean experience.	Singapore Medical Journal 1999; 40(12): 752-755
Meta-analyses		
Al Inany et al (2006)	Gonadotrophin-releasing hormone antagonists for assisted contraception.	Cochrane Database of Systematic Reviews Issue 3 [Art. No.: CD001750. DOI: 10.1002/14651858.CD001750.pub2]
Kolibianakis et al (2006)	Among patients treated for IVF with gonadotropins and GnRH analogues, is the probability of live birth dependant on the type of analogue used? A systematic review and meta-analysis.	Human Reproduction Update 2006; 12(6): 651-671
Franco Jr. et al (2006)	GnRH agonist versus GnRH antagonist in poor ovarian responders: A meta-analysis.	Reproductive BioMedicine Online 2006; 13(5): 618-627
Griesinger et al (2006)	GnRH-antagonists in ovarian stimulation for IVF in patients with poor response to gonadotropins, polycystic ovary syndrome, and risk of ovarian hyperstimulation: A meta-analysis.	Reproductive BioMedicine Online 2006; 13(5): 628-638

8. Results of Trials

Comparative effectiveness

The meta-analysis of analogue stimulation versus non-analogue stimulation found a statistically significant advantage for analogue stimulation in clinical pregnancy rate (RD=7.98%; 95% CI: 3.76%, 12.20%).

The PBAC considered this advantage for analogue stimulation should be interpreted with caution given that there was a wide range of effect across the trials, with a number of different drugs and doses used and varying patient characteristics. The PBAC noted some studies used human menopausal gonadotropin (hMG), FSH, FSH-hMG as the non-analogue arm while the analogue differed in drug, doses and duration. While these various options may have been used clinically at the time of the studies, it made the meta-analysis highly uncertain because of a whole range of confounding factors and thus must be treated with caution. In addition, neither ganirelix nor nafarelin were included in any of the analogue trials.

The table below provides the results of the head-to-head trial comparing ganirelix and nafarelin (Rombauts et al., 2006). This trial focused on the use of oral contraceptive (OC) pre-treatment and included two ganirelix treatment arms, one with OC treatment and one without.

Results of efficacy outcomes across the direct randomised trial

Outcomes	Ganirelix + OC mean ± SD	Ganirelix mean ± SD	Nafarelin mean ± SD	p-value
Rombauts et al (2006)	N=111	N=110	N=111	
Primary outcomes				
No. of oocytes recovered per attempt	13.1 ± 7.8	11.5 ± 7.6	12.9 ± 8.7	NS[a]
No. of good quality embryos obtained	5.1 ± 3.8	5.0 ± 4.5	5.7 ± 4.3	NS[a]
Key secondary outcomes				
Duration of rFSH (treatment days±SD)	11.7 ± 1.9	9.4 ± 1.6	10.3 ± 1.7	≤0.001[a]
Total rFSH dose (IU)	2667.0 ± 880.7	1965.7 ± 515.5	2221.8 ± 655.3	≤0.001[a]
No. of GnRH analogue treatment days	4.6 ± 1.6	4.5 ± 1.3	27.0 ± 3.7	-
Fertilisation rate % (SD)	61.2% (25.7)	66.7% (24.7)	64.7% (23.7)	-
Number of LH rises n (%)	2 (1.7%)	17 (14.5%)	1 (0.8%)	≤0.001[b]
Implantation rate per transfer % (SD)	12.3% ± 27.3	17.4% ± 30.8	21.6% ± 33.4	0.03[c]
Ongoing pregnancy rate per attempt n (%)	18 (16.2%)	23 (20.9%)	26 (23.9%)	NS[a]

SD = standard deviation; NS = not significant p>0.05
[a] All pairwise comparisons.
[b] Ganirelix alone compared with ganirelix + OC and nafarelin groups.
[c] Ganirelix + OC compared with nafarelin group.

The PBAC noted that there were no statistically significant differences between the ganirelix groups and nafarelin in the patient-relevant outcome of ongoing pregnancies. There were statistically significant differences between all groups in duration and total rFSH use. The ganirelix group with the scheduled oral contraceptive required significantly more rFSH than the other groups while the group administered ganirelix alone required significantly less than others. The PBAC noted that it is not known what percentage of patients would use the combination of ganirelix with oral contraceptive in practice. Compared with other groups, the participants administered ganirelix without the OC experienced significantly more LH rises. This was a concern for the PBAC as the prevention of LH rises is a key reason for the use of a GnRH analogue.

The results of the supportive indirect comparison using leuprolide as the common reference found no statistically significant difference between ganirelix and nafarelin in clinical pregnancy rate (RR=1.06; 95% CI: 0.58, 1.95). However, the wide confidence interval, potentially stemming from the small population size in the trials, indicated that the relative risk was somewhat imprecise and should be interpreted with caution. The PBAC noted that the ganirelix trials were conducted after the year 2000 whereas all the nafarelin trials were conducted before the year 2000. The success rates for leuprolide in the ganirelix trials were generally higher than in the nafarelin trials which may indicate improvement in technique over the five year period between the two groups of studies.

The PBAC noted that the results of the meta-analyses summarised by the submission, which included a range of antagonists (including ganirelix) and a range of agonists (including nafarelin) were conflicting, with one reporting equi-efficacy between antagonists and agonists for live birth rate Kolibianakis et al (2006) while a Cochrane review (Al Inany et al

2006) reports that antagonists had statistically significantly lower rates of clinical pregnancy and ongoing pregnancy/live birth rate compared to agonists.

Comparative toxicity
In the comparison of ganirelix with nafarelin, the Rombauts et al (2006) trial reported numerically higher numbers of adverse events including ovarian hyperstimulation syndrome (OHSS) in the nafarelin group, with the exception of serious adverse events, which occurred with greater frequency in the OC and ganirelix group. No statistical comparison of adverse events was provided and the trial was not powered to detect statistically significant differences between groups in rates of OHSS. Only three of the trials included in the indirect comparison provided safety information. The extended assessment of comparative harms in the submission did not enable conclusions as to comparative adverse event rates to be made.

9. Clinical Claim

The submission described GnRH analogue use in COS as superior in terms of comparative effectiveness (clinical pregnancies) and made no statement about comparative safety over non-analogue treatment in COS.

The submission described ganirelix as similar in terms of comparative effectiveness (pregnancy outcomes) and superior in terms of comparative safety over nafarelin.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

A stepped economic evaluation was presented. The type of analysis was a cost-effectiveness analysis and the submission presented a comparison of analogue versus non-analogue stimulation and a comparison of ganirelix versus nafarelin.

Step 1 of the evaluation was a trial-based analysis and step 2 was an extrapolation of this over six cycles.

The model was driven by rates of clinical pregnancies (efficacy) and drop-outs. The model was sensitive to changes in efficacy and to increased FSH use.

The base case incremental cost per clinical pregnancy of the analogue versus non-analogue comparison was dominant for analogue stimulation. The base case incremental cost per clinical pregnancy of the ganirelix versus nafarelin comparison was estimated to be less than $15,000.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of packs dispensed per year to be between 10,000 and 50,000 in Year 5. The financial cost per year to the PBS was estimated to be <$10 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended the listing of ganirelix on the PBS in the Section 100 IVF/GIFT Program for the prevention of premature luteinisation and ovulation in patients undergoing

controlled ovarian stimulation, followed by oocyte pick-up and assisted reproductive techniques, at the same price as nafarelin acetate for the treatment of endometriosis, which equates to a cost of DPMQ $95.51 x 2 per patient per fresh cycle of assisted reproduction technique (ART).

The PBAC considered this is a pragmatic way forward in the context of a clinical need, considering that gonadotrophin releasing hormone (GnRH) analogues are commonly used in current clinical practice, and considering the evidence as a whole presented in the submission suggests that GnRH analogues are effective agents in ART and that ganirelix and nafarelin are of similar efficacy and safety. The PBAC also noted that the cost effectiveness of nafarelin in ART is unknown as nafarelin is not listed on the PBS for ART. The PBAC considered insufficient evidence was provided to substantiate the claim that ganirelix is of superior comparative safety to nafarelin.

The PBAC considered the economic evaluation presented in the submission was highly uncertain. The submission's claim that patients treated with ganirelix would use less follicle stimulating hormone (FSH) than patients being treated with nafarelin was highly uncertain and FSH use may be dependant on whether oral contraceptives are used. The PBAC considered it was inappropriate to use the metric of an incremental cost per discounted "life year created" considering the lack of reference to this metric in the published literature. The Committee also considered it was not appropriate to include incremental differences in dropout rates between ganirelix and nafarelin in the economic evaluation based on a better adverse event profile for ganirelix, as the evidence did not provide a sufficient base to support the claim of superior safety of ganirelix over nafarelin. Furthermore, although ganirelix may appear to be superior to nafarelin in terms of incidence of ovarian hyper-stimulation syndrome (OHSS), OHSS is a very rare event and there were insufficient data to draw any conclusions in this regard.

The assumption that the clinical pregnancy rate is 7.98 % higher with analogues compared to non-analogues adds to the uncertainty in the economic model. Further, the meta-analysis performed in the submission comparing analogues to non-analogues is highly uncertain as the source data do not include nafarelin or ganirelix-treated patients. Additionally, there was a potential for considerable heterogeneity between the trials.

The PBAC considered listing in the Section 100 IVF/GIFT program of nafarelin and cetrorelix for ART on the same basis as ganirelix may be appropriate and would be willing to consider submissions from the respective sponsors of nafarelin and cetrorelix to this effect.

Recommendation:
GANIRELIX, solution for injection, 250 micrograms in 0.5 mL (as acetate), single use pre-filled syringe and 5 pre-filled syringes

Restriction:

NOTE: Arrangements to prescribe this item should be made by medical practitioners with Medicare Australia, contact telephone number 1800 700 270.

Section 100 (IVF/GIFT PROGRAM)
For the prevention of premature luteinisation and ovulation in patients undergoing controlled ovarian stimulation, followed by oocyte pick-

up and assisted reproductive techniques as described in item 13200 of the Medicare Benefits Schedule.

Pack size: 1 (250 micrograms in 0.5 mL)

Pack size: ♯1 (250 micrograms in 0.5 mL (5))

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

The sponsor has no comment.