PUBLIC SUMMARY DOCUMENT
Product: DEGARELIX, powder for subcutaneous injection (modified release), 80 mg and 120 mg, (as acetate) with solvent, syringe and needles, Firmagon®
Sponsor: Ferring Pharmaceuticals Pty Ltd
Date of PBAC Consideration: July 2010

1. Purpose of Application
To seek an Authority Required listing for the treatment of locally advanced (equivalent to stage C) or metastatic (equivalent to stage D) carcinoma of the prostate.

2. Background
This drug had not been previously considered by the PBAC.

3. Registration Status
Degarelix was TGA registered on 16 February 2010 for treatment of patients with prostate cancer in whom androgen deprivation is warranted.

4. Listing Requested and PBAC's View
Authority Required
Locally advanced (equivalent to stage C) or metastatic (equivalent to stage D) carcinoma of the prostate.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy
Prostate cancer, localised within the prostate gland, can be treated successfully with surgery or radical radiotherapy. However, 30% of patients will develop metastatic disease. The current endocrine therapy, including the blockade of androgen receptors (anti-androgen therapy) and indirect inhibition of the biosynthesis of androgen (gonadotropin releasing hormone (GnRH) agonist therapy), is the first and primary means of treatment for patients with metastatic prostate cancer.

Degarelix is a GnRH receptor antagonist and unlike the GnRH agonists does not induce a luteinising hormone (LH) surge with subsequent testosterone surge/tumour stimulation and symptomatic flare after the initiation of treatment. It will provide an alternative treatment option for the treatment of prostate cancer.

6. Comparator
The submission nominated leuprorelin acetate, 7.5 mg, powder for I.M injection as the main comparator. This was considered reasonable by the PBAC.

7. Clinical Trials
The submission presented one randomised trial, Trial CS21 comparing subcutaneous injections of degarelix 240 mg initially, then 80 mg every 28 days (referred to as 240/80 mg) with intramuscular injections of leuprorelin 7.5 mg given every 28 days in patients with Stage C or D prostate cancer for 12 months.

This trial had been published at the time of submission as follows:

Trial ID/First author	Protocol title	Publication citation
CS21 Klotz et al (2008).	The efficacy and safety of degarelix: a 12-motnh, comparative, randomised, open-label, parallel-group phase III study in patients with prostate cancer.	British Journal of Urology International 2008; 102(11): 1531-8.

8. Results of Trials

The primary outcome of Trial CS21 was the difference between degarelix and leuprorelin of the cumulative probabilities of maintaining testosterone ≤0.5 ng/mL from Day 28 to Day 364. Results were summarised for both the treated patient population, of all patients who received at least one dose of the medication, and the per protocol (PP) patient population.

Cumulative probability of testosterone ≤0.5 ng/mL from Day 28 to Day 364 – Kaplan-Meier estimates of individual response rates

Trial CS21	Degarelix 240/80 mg n (%) [95% CI]	Leuprorelin 7.5 mg n (%) [95% CI]	Difference to Leuprorelin (%) [97.5% CI]
Treated population Response rate[a]	N=207 202 (97.2%) [93.5;98.8%]	N=201 194 (96.4%) [92.5;98.2%]	(0.9%) [-3.2;5.0%]
PP population Response rate	N=200 195 (97.2%) [93.3;98.8%]	N=195 188 (96.3%) [92.4;98.2%]	0.9% [-3.3;5.1%]

Abbreviations: treated population = patients who received at least one dose of the medication; PP=per protocol population.

The cumulative probability of testosterone ≤0.5 ng/mL from Day 28 to Day 364 was high in both the degarelix and leuprorelin treatment groups, the lower bound 95% CI for both the treated and the PP patient populations were above 90%. The submission claimed that according to the U.S Food and Drug Administration (FDA) efficacy criteria, this demonstrates that both degarelix and leuprorelin were effective in achieving and maintaining testosterone at castrate levels (≤0.5 ng/mL) from Day 28 through Day 364.

Comparing patients treated with degarelix and leuprorelin, the difference in cumulative probability of testosterone ≤0.5 ng/mL between the two groups was 0.9% (95% CI: -3.2, 5.0%) and 0.9% (95%CI: -3.3, 5.1%) in the treated and PP populations respectively. The submission claimed that Trial CS21 demonstrated that treatment with degarelix 240/80 mg was non-inferior to leuprorelin 7.5 mg therapy in achieving and maintaining testosterone ≤ 0.5 ng/mL from Day 28 through Day 364 for both the treated and PP analysis sets.

The submission presented the results of secondary outcomes of the proportions of patients with testosterone level ≤ 0.5 ng/mL at Day 3 and the proportions of patients who demonstrated a testosterone surge during the first two weeks of the trial, and median percent change in prostate specific antigen (PSA) levels from Day 0 to Day 14 and Day 28 of Trial CS21.

The results illustrated that more rapid suppression of PSA and testosterone levels occurred in patients treated with degarelix compared to patients treated with leuprorelin. The submission

provided no evidence to demonstrate whether the prevention of a testosterone surge and/or the more expediant reduction in PSA levels in the first month of possible long-term treatment with degarelix would have significant effects on patient relevant outcomes such as disease progression or overall survival compared with leuprorelin.

For PBAC's view, see Recommendation and Reasons.

The incidence of adverse events was similar for patients treated with degarelix 240/80 mg (79%) and leuprorelin 7.5 mg (78%) RR (95%CI): 1.01 (0.92, 1.12), p value=0.78. There were no significant differences between degarelix 240/80 mg and leuprorelin 7.5 mg arms in the incidence of serious AEs (10% vs. 14%, p value=0.24), deaths (2% vs. 4%, p value = 0.26) and adverse events leading to discontinuations (7% vs. 6%, p value = 0.60). However, significantly more patients treated with degarelix 240/80 mg (57%) reported adverse drug reactions (ADRs) compared with patients treated with leuprorelin (42%), RR (95% CI): 1.36 (1.12, 1.67), p value = 0.003. The majority of treatment-emergent ADRs were general disorders and administration site conditions including injection-site reactions which occurred in 73 (35%) patients in the degarelix 240/80 mg group compared with 1 patient (0.5%) in the leuprorelin arm (RR(95%CI): 70.88 (9.95, 505.13); p value < 0.0001).

9. Clinical Claim

The submission described degarelix as non-inferior in terms of comparative safety and non-inferior in terms of comparative effectiveness:

- Over leuprorelin 7.5 mg for Days 28 to 364 for the maintenance dose of degarelix 80 mg and
- Over leuprorelin 7.5 mg in combination with an anti-androgen for Days 0 to 28 for initiation dose of degarelix 240 mg.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses were estimated for maintenance therapy (Days 28 onwards): degarelix 80 mg monthly vs. leuprorelin 7.5 mg monthly; and for initiation therapy (Days 0 to 28): degarelix 240 mg vs. leuprorelin 7.5 mg in combination with a bicalutamide (50 mg).

The submission did not consider potential costs associated with any co-administered pain relief with degarelix to account for injection site reactions in the cost minimisation analysis.

The PBAC did not accept that bicalutamide would be used in all patients commenced on leuprorelin. *See Recommendation and Reasons.*

11. Estimated PBS Usage and Financial Implications

The drug cost/patient/year was estimated by the submission based on one starter pack of 2x120 mg injections and 11 monthly injections of 80 mg.

The likely number of packs dispensed per year was estimated by the submission to be between 10,000 and 50,000 in Year 5. The submission's estimate may be uncertain due to assumptions about the degarelix market share and/or market growth.

The net financial cost to the PBS, based on the submission's assumptions, was estimated to be zero.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC recommended listing of degarelix on the PBS as an Authority Required (STREAMLINED) listing for locally advanced (equivalent to stage C) or metastatic (equivalent to stage D) carcinoma of the prostate on a cost-minimisation basis compared with leuprorelin acetate 7.5 mg powder for I.M. injection. The equi-effective doses are for maintenance therapy (Days 28 onwards) degarelix 80 mg monthly and leuprorelin 7.5 mg monthly, and for initiation therapy (Days 0 to 28) degarelix 240 mg and leuprorelin 7.5 mg, in combination with bicalutamide (50 mg) daily for 11% patients.

The PBAC noted that the current restrictions for anti-androgens permit combination use with GnRH agonists only. The PBAC considered that there was no reason to preclude degarelix (an GnRH antagonist) from use in combination with the currently PBS listed anti-androgens as there was a clinical need in certain patients for total androgen blockade and requested the Secretariat to write to those sponsors informing them of the proposed change.

The PBAC noted that the submission assumed that all patients started on leuprorelin would receive an anti-androgen. However, only 11% of the patients in Trial CS21 were co-administered anti-androgens with leuprorelin and the PBAC considered this to be a reasonable reflection of current clinical practice. The PBAC noted that testosterone surge may not be a relevant consideration for patients switching to degarelix therapy after established androgen deprivation therapy and guidelines indicate that anti-androgens are only indicated with GnRH agonists in patients with features such as impending spinal cord compression or urinary obstruction (Loblaw et al 2004). The PBAC considered the DUSC estimate of 19.2 % to be overestimated as it captured people with a script for a peripheral anti-androgen blockade 2 months prior to and 12 months post leuprorelin. However, for flare prevention the anti-androgen should have preceded or at least been given concurrently with goserelin.

The PBAC accepted that use of testosterone levels as a surrogate outcome was reasonable and that degarelix was non-inferior in terms of efficacy compared with leuprorelin. However, the PBAC noted that there are more injection site reactions compared with leuprorelin and therefore degarelix may not be non-inferior with regards to safety.

The PBAC noted that there was potential for increased costs to the Government if degarelix, given monthly, was substituted for GnRH agonists, given 3 monthly, requiring extra visits to the doctor or nurse practitioner. The PBAC noted that currently most patients receive an injection of a GnRH agonist at intervals of 3 months or more. Therefore, the PBAC considered that any additional costs associated with the administration of degarelix should be included in the cost-minimisation of degarelix versus leuprorelin.

Recommendation:

DEGARELIX, powder for subcutaneous injection (modified release), 80 mg and 120 mg, (as acetate) with solvent, syringe and needles, Firmagon®

Restriction:	Authority Required (STREAMLINED) Locally advanced (equivalent to stage C) or metastatic (equivalent to stage D) carcinoma of the prostate. NOTE: No applications for increased maximum quantity and/or repeats will be authorised for the 120 mg powder for injection.
Maximum quantity:	‡1 (120 mg, 2 vials) 1 (80 mg)
Repeats:	Nil (120 mg) 5 (80 mg)

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 Degarelix (FIRMAGON) for patients with locally advanced (equivalent to stage C) or metastatic (equivalent to stage D) carcinoma of the prostate.