Response to:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Degarelix for treating advanced hormone-dependent prostate cancer

Prepared by:

Ferring Pharmaceuticals Limited

3 February 2014

Response to the Appraisal Consultation Document (ACD): Degarelix for treating advance hormone-dependent prostate cancer

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Academic in confidence information is highlighted and underlined, e.g. XXXXXX

Any reference to the ACD is referred to in the format: [page X, Section X.X]

Approved Name of Medicinal Product:	degarelix
Brand Name:	Firmagon®
Company:	Ferring Pharmaceuticals
Date:	31 January 2014

Letter of address

Dear Kate,

We would like to take this opportunity to thank NICE for the time and consideration the Appraisal Committee (AC) and the support teams have devoted to this submission process. However, upon reviewing the Appraisal Consultation Document (ACD), Ferring considers the ACD recommendation is too restrictive with respect to the prostate cancer population that is covered based on the evidence presented to the AC and in the context of the approved label.

The ACD raises issues regarding the appropriateness of the pooled analyses, treatment pathway algorithm and utility mapping algorithm that formed part of the original submission. To address these concerns, additional meta-regression analyses (which show no sign of trial heterogeneity) to support the significant efficacy and safety benefits of degarelix, as well as the inclusion of the requested changes to the treatment pathway algorithm and utility mapping have been completed and provided within this response and are detailed in **Appendix A**. These analyses indicate the ICER from the updated model is still below the recognised threshold for a cost-effective treatment.

Based upon the further analyses presented within this response, in conjunction with the original submission, Ferring considers there to be a strong evidence base demonstrating that those patients at high risk of prostate-specific antigen (PSA) progression and/or with pre-existing cardiovascular disease (CVD) represent additional populations that would particularly benefit from treatment with degarelix. Ferring requests the AC to reconsider the recommendation in light of the following information detailed within this response document:

1. **PSA progression**

   It would appear the AC exhibits a degree of uncertainty, with respect to the improved PSA progression-free survival (PSA PFS) observed for degarelix versus LHRH agonists.[1-3], with the ACD stating *'The Committee concluded that the results for PSA progression and long-term PSA progression benefit for degarelix compared with LHRH agonists were highly uncertain and therefore no PSA progression benefit from degarelix compared with LHRH agonists could be assumed'* **[page 30, section 4.7]**. Within this response, Ferring provides further clarification of the differential mechanism of action of degarelix, versus luteinising hormone-releasing hormone (LHRH) agonists, and the subsequent impact this is likely to have on PSA

progression. These explanatory rationales did not appear to be fully considered in either the ACD or the preceding AC meeting. This ACD response also restates the pivotal findings of the Phase III extension trial (CS21A), which support the statistically significant PSA PFS benefit for degarelix over leuprorelin seen during the first year of treatment.[3] In addition, we have provided reference to further analyses of this extension study over five years, which demonstrate the significant PSA PFS benefit established for degarelix during year one remained consistent at five years (detailed **Appendix A, Section 1**). We have provided this information in our response, particularly due to the fact that not all members present at the AC meeting had been provided the submission appendices by NICE, which detail supporting RCT information. In addition, a meta-regression analysis (that demonstrates no sign of trial heterogeneity) of PSA PFS from CS21 and CS35 trial data has been completed (detailed in **Appendix A, Section 2**).

2. Cardiovascular data

During the AC meeting held on 27 November 2013, it was made apparent from discussions that not all of the panel members had reviewed, in full, the evidence presented by Ferring showing the reduced risk of cardiovascular (CV) serious adverse events (SAEs) and death in patients with CV disease (CVD) at baseline in those treated with degarelix versus LHRH agonists. Ferring would like to take this opportunity to reiterate the relevance of the recent, independently produced, peer-reviewed publication by Albertsen *et al* 2013.[4] The conclusions of this paper present the full impact and clinical importance of the reduced risk of CV SAEs and death of degarelix versus LHRH agonists. To highlight, again, the benefits of degarelix with respect to an improved CV SAE and death risk in patients with existing CVD to the AC, the findings from Albertsen *et al* 2013[4] have been described in this ACD response.

In addition, the meta-regression analysis, as recommended within the ACD **[page 20, section 3.2.4]**, that evaluates the risk of CV SAEs and death in patients with pre-existing CVD is presented (as **Appendix A, Section 2**). This analysis demonstrates that there is no sign of trial heterogeneity and adjusted hazard ratios are used in the updated economic model. The results of this meta-regression analysis are in line with those from the pooled analysis and Albertsen *et al* 2013[4] that formed part of the original submission. Such benefits can be put into the context of other treatments used in a high-risk CVD population; for example, over a 5.4 year median follow-up period the relative risk of a major coronary event (coronary death, non-fatal definite

or probable myocardial infarction [MI], silent MI or resuscitated cardiac arrest) in those treated with a statin (simvastatin) versus placebo was 0.66 (95% CI 0.59-0.75; p<0.00001).[5]

The significantly reduced CV and death risk that degarelix offers, compared with LHRH agonists, is of particular relevance to the decision problem, as the population covered by the licensed indication of degarelix has a high prevalence of CV co-morbidity; indeed, in England the prevalence of CVD for those aged 65–74 and ≥75 years, the age groups with the highest incidence of prostate cancer,[6] is 34.1% and 44.4%,[7] respectively. In light of the high prevalence of CVD in the prostate cancer population, Ferring felt it was appropriate to reiterate and further clarify the clinical evidence available to support the adverse event (AE) safety benefits of degarelix with respect to CV risk within this ACD response.

3. Subgroups of greatest benefit

It is requested that, based on feedback from clinicians and patient representatives, the committee reconsiders patient access to degarelix in the context of the prostate cancer clinical guideline (CG175) including:

A) The recommendations for hormonal therapy in the total metastatic prostate cancer population, and

B) The evaluation of the risk of cardiovascular side effects of androgen deprivation therapy.

It is our judgement, that the initial focus on the immediate suppression benefit of degarelix to only those at risk of spinal cord compression (SCC) lent undue weight to discussions held during the AC meeting and a lack of credit or weight was placed on the other subgroups highlighted within the ACD; e.g., *'The clinical specialists also highlighted that degarelix is particularly appropriate for people at high risk of disease progression (that is, with a prostate-specific antigen [PSA] level of more than 20 ng/ml), for people with spinal metastases who are at risk of impending spinal cord compression, older people and those with pre-existing cardiovascular disease*' **[page 27, section 4.2]**. Furthermore, whilst we note that the immediate suppression of testosterone offered by degarelix is of benefit to those at risk of SCC, this clinical efficacy characteristic is also of benefit to a wider population, i.e. all patients at risk of, or suffering from, symptomatic disease, including those with bone pain and/or bone metastases and/or bladder outlet obstruction (BOO).

4. Meta-regression analyses

Ferring recognises that the evidence review group (ERG) advice states that *'It considered this* [use of pooled analyses] *to be inappropriate because such pooling ignores the characteristics of individual studies and relies on the assumption that there is no difference between individual trials. The ERG suggested that meta-analyses would have been more appropriate to maintain the effects of randomisation and ensure that each study acts independently, minimising the impact of potential confounding variables. Therefore, the ERG considered that the results presented in pooled analyses in the manufacturer's submission (see section 3.11) were inappropriate and should be interpreted with caution'* **[page 20, section 3.2.4].** To address the uncertainty about possible differences between individual trials, we present within **Appendix A, Section 2** of this response the following meta-regression to re-confirm the efficacy and safety analysis results by adopting the preferred methodology from NICE/AC (see **Table 1**).

Table 1. Detail of meta-regression analyses within Appendix A of this response

Endpoint	Studies included	Subgroup	Table in Appendix A, Supplementary information 2
PSA PFS	CS21 and CS35*	Overall, FAS	Table 2.1
PSA PFS	CS21 and CS35*	PSA >20 ng/ml, FAS	Table 2.2
PSA PFS	CS21 and CS35*	Advanced prostate cancer (metastatic or locally advanced), FAS	Table 2.3
JSS	CS21, CS28, CS30, CS31, CS35 and CS37**	Overall, Safety Analysis Set	Table 2.4
JSS	CS21, CS28, CS30, CS31, CS35 and CS37**	PSA >20 ng/ml, Safety Analysis Set	Table 2.5
Fractures	CS21, CS28, CS30, CS31, CS35 and CS37**	Overall, Safety Analysis Set	Table 2.6
Fractures	CS21, CS28, CS30, CS31, CS35 and CS37**	PSA >20 ng/ml, Safety Analysis Set	Table 2.7
CV SAE excluding death	CS21, CS28, CS30, CS31, CS35 and CS37**	CVD population, Safety Analysis Set	Table 2.8
CV SAE including death	CS21, CS28, CS30, CS31, CS35 and CS37**	CVD population, Safety Analysis Set	Table 2.9

* It is relevant to only pool CS21 and CS35 trials for purposes of evaluating PSA PFS, since only these two trials evaluated PSA failure using the same clinically relevant criterion, which is subsequently used to re-derive PSA PFS
**All data from the intermittent degarelix arm in CS37 is censored at month 7, i.e. the data from CS37 used within meta-regression analyses only included patients with a continuous therapy.
Abbreviations: PSA PFS: prostate specific antigen progression-free survival; JSS: Joint-related signs and symptoms; CV: cardiovascular; SAE: serious adverse event; FAS; full analysis set

We trust the provision of these extensive meta-analyses (detailed within **Appendix A, Section 2**) addresses the uncertainties that the AC committee hold and provides further corroboration of the differential efficacy and safety benefits degarelix has over LHRH agonists.

5. Clinical pathway treatment algorithm

Ferring recognises that the AC does not fully agree with the treatment algorithm provided, with the ACD stating *'The clinical specialists also stated that, in clinical practice, treatment with LHRH agonists continues after the disease progresses until death. The clinical specialists noted that the treatment pathway for people with advanced prostate cancer is changing; hormonal treatment is being given earlier,*

drugs such as enzalutamide and abiraterone are used after disease progression, and treatment with abiraterone is increasingly being considered before chemotherapy in the treatment pathway' **[page 26, section 4.2]**. To confirm, our reasoning behind excluding enzalutamide and placing abiraterone after docetaxel was to adhere to current NICE recommendations[8] at the time of submission, which is a stipulated requirement of STA submissions. However, we recognise that representing clinical practice is of great value, in terms of informing decision-making by the AC; therefore, within **Appendix A, Section 3** of this ACD response, we have provided additional cost-effectiveness analyses including:

1. A scenario analysis to evaluate the introduction of enzalutamide into the treatment algorithm (plus sensitivities around patient proportions receiving this treatment)
2. A scenario analysis to evaluate the placement of abiraterone prior to docetaxel following disease progression (plus sensitivities around patient proportions receiving these treatments)
3. Modelling treatment with LHRH agonists/degarelix until death within the base case.

We trust that the provision of these scenario analyses answers the voiced concerns with respect to the treatment pathway algorithm and aid the AC's re-evaluation of degarelix. These analyses, **Appendix A, Section 3** of this response, indicate the ICER from the updated model, which has the suggestions from the AC and ERG incorporated, is still below the recognised threshold for a cost-effective treatment.

6. Additional quality of life and utility mapping activities

We note that the ACD states the use of the Kontodimopoulos *et al.* (2009)[9] utility mapping algorithm as inappropriate *'The Committee considered that an alternative algorithm considered by the manufacturer, from McKenzie and van der Pol (2009),[10] was more appropriate….'* **[page 36, section 4.16]** and describes how the manufacturer did not provide a probabilistic estimate of the incremental cost-effectiveness ratio (ICER) *'It noted that the results were based on a deterministic estimate of the ICER and that the manufacturer did not provide a probabilistic estimate of the ICER'* **[page 36, section 4.16]**. Within **Appendix A, Section 3** of this response, Ferring has addressed these concerns and provided utility mapping using the alternative, suggested algorithm by the AC (McKenzie and van der Pol 2009)[10] and provided the requested probabilistic estimates of the ICER. These analyses,

indicate the ICER from the updated model, which has the suggestions from the AC and ERG incorporated, is still below the recognised threshold for a cost-effective treatment.

This response aims to demonstrate the value of degarelix, and provide further clarification on the efficacy and safety benefits of degarelix versus LHRH agonists. Based upon the additional analyses presented within **Appendix A** of this response, in combination with the original submission, there is a firm evidence base supporting that those patients at high risk of PSA progression and/or with pre-existing cardiovascular disease (CVD) represent additional populations that would particularly benefit from treatment with degarelix.

Ferring requests the AC to reconsider the ACD recommendation and broadens the prostate cancer population for which degarelix is recommended to ensure the widest choice of treatments is available to both clinicians and patients. We look forward to attending the AC meeting on the 11th February 2014, to help increase patient access to this valuable medicine in the NHS.

Yours sincerely,

[redacted]

References

1. Tombal B, Miller K, Boccon-Gibod L *et al*. Additional analysis of the secondary end point of biochemical recurrence rate in a phase 3 trial (CS21) comparing degarelix 80 mg versus leuprolide in prostate cancer patients segmented by baseline characteristics. *Eur Urol* 2010; **57:** 836–842.
2. Klotz L, Miller K, Crawford DE *et al*. Disease control outcomes from analysis of pooled individual patient data from five comparative randomised clinical trials of degarelix versus luteinising hormone-releasing hormone agonists. *Eur Urol* 2014**:** [Submitted].
3. Crawford ED, Tombal B, Miller K. A Phase III extension trial with a 1-arm crossover from leuprolide to degarelix: Comparison of gonadotropin-releasing hormone agonist and antagonist effect on prostate cancer. *J Urol* 2011; **186:** 889-897.
4. Albertsen PC, Klotz L, Tombal B *et al*. Cardiovascular Morbidity Associated with Gonadotropin Releasing Hormone Agonists and an Antagonist. *Eur Urol* 2013**:** [Epub ahead of print].
5. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; **344:** 1383-1389.
6. Office for National Statistics. Cancer statistics registrations, England (Series MB1), No. 42 www.ons.gov.uk/ons/rel/vsob1/cancer-statistics-registrations--england--series-mb1-/no--42--2011/rft-main-tables.xls (last accessed 08 January 2014)
7. British Heart Foundation. *Coronary heart disease statistics: a compendium of health statistics, 2012 edition.* London: BHF, 2012.
8. National Institute for Health and Care Excellence. *Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen. Technology Appraisal TA259*. London: NICE, 2012. http://guidance.nice.org.uk/TA259 (last accessed 08 January 2014)
9. Kontodimopoulos N, Aletras VH, Paliouras D, Niakas D. Mapping the cancer-specific EORTC QLQ-C30 to the preference-based EQ-5D, SF-6D, and 15D instruments. *Value Health* 2009; **12:** 1151-1157.
10. McKenzie L, van der Pol M. Mapping the EORTC QLQ C-30 onto the EQ-5D instrument: the potential to estimate QALYs without generic preference data. *Value Health* 2009; **12:** 167-171.