NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Degarelix for treating advanced hormone-dependent prostate cancer [ID590]

Dear [redacted]

The Evidence Review Group, School of Health and Related Research (ScHARR), and the technical team at NICE have now had an opportunity to take a look at the submission received on the Thursday 29 August 2013 by Ferring Pharmaceuticals. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on **Friday 04 October 2013**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Pilar Pinilla-Dominguez, Technical Lead (pilar.pinilla-dominguez@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (kate.moore@nice.org.uk) in the first instance.

Yours sincerely

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Section A: General requests

A1. **Priority request:** Please provide evidence supporting the validity of the description of the clinical pathway and a justification for the assumption of the proportion of patients whose disease fails each treatment and continue with another line of therapy. The ERG has received advice from clinical experts that the current treatment pathway illustrated in Figure 2 (page 20 of the manufacturer's submission) does not accurately reflect clinical practice.

A2. Please clarify further Section 2.6 (page 21) by describing any variations or uncertainty relating to current clinical practice.

Section B: Clarification on literature searching

B1. **Priority request**: Please provide the search strategies for Medline, Medline in-Process, Embase and Web of Science which are absent in Appendix 2 (page 231).

B2. **Priority question**: The Cochrane Library search strategy supplied for Section 6.1 "Identification of studies" (page 232) does not contain any subject-headings. Please confirm if MeSH subject headings and Emtree thesauri terms were included in Medline and Embase search strategies, respectively.

B3. **Priority request:** Please provide the inclusion/exclusion criteria for the identification of the studies for the mixed treatment comparison (MTC; Section 6.7.1, page 81) and the resulting flow diagram for the MTC.

B4. In the flow diagram (page 38 of the manufacturer's submission), please clarify whether the Cochrane Central Register of Controlled Trials records were included in the 2237 (1862 + 375) records from the database searches before duplicates were removed.

B5. Please clarify reasons for omission of the following studies from the manufacturer's submission. If any of the trials were identified and subsequently excluded from the searches in the submission please state the explicit reasons for exclusion:

Clinical trial no.	Trial Title	Status	Enrollment	Sponsor/Collaborators
NCT00117949	Study Investigating the Pharmacokinetics, Pharmacodynamics and Safety of FE200486	Completed 2004 Has Results	82	Ferring CS06
NCT00117312	Extension Study Investigating the Long-Term Safety and Tolerability of Repeat Doses of FE200486 in Prostate Cancer Patients	Terminated 2005 Has Results	37	Ferring CS06A
NCT00818623	Investigation of a New Trial Drug (FE200486) in Prostate Cancer Patients	Completed 2004 Has Results	172	Ferring CS07
NCT00245466	Study Investigating the Long-Term Safety and Tolerability of Repeated Doses of Degarelix in Prostate Cancer Patients	Terminated 2006 Has Results	88	Ferring CS02A

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NCT002 15657	Extension Study Investigating the Long-Term Safety and Tolerability of Repeat Doses of FE200486 in Prostate Cancer Patients	Terminated 2006 Has Results	131	Ferring CS07A
NCT001 17286	Extension Study Investigating the Long-Term Safety of Degarelix One-Month Depots in Patients With Prostate Cancer	Completed 2009 Has Results	57	Ferring CS14A
NCT010 71915	Efficacy and Safety of Degarelix One Month Dosing Regimen in Korean Patients With Prostate Cancer	Completed 2011 Has Results	157	Ferring CS42
NCT012 20869	A Study of Degarelix in Taiwanese Patients With Prostate Cancer	Completed 2012 No Results Available	110	Ferring CS43
NCT007 38673	Degarelix as Second-Line Hormonal Treatment After Prostate-specific Antigen (PSA)-Failure in GnRH Agonist Treated Patients With Prostate Cancer	Completed 2011 Has Results	37	Ferring CS27
NCT008 01242	Intermittent Treatment With Degarelix of Patients Suffering From Prostate Cancer	Completed 2013 No Results Available	220	Ferring CS29
NCT014 91971	Intramuscular Injections of Degarelix Administered in 1-Month Dosing Regimens in Patients With Prostate Cancer	Completed 2012 No Results Available	76	Ferring
NCT013 44564	Initiation of Androgen Deprivation Therapy for Prostate Cancer Using Degarelix Followed by Leuprolide	Completed 2012 No Results Available	50	Urology of Virg inia/ Ferring

Section C: Clarification on effectiveness data

C1. **Priority request**: Please provide results of the MTC including bicalutamide as a comparator. If it is not possible to undertake a naïve indirect comparison for bicalutamide (with appropriate subgrouping from CS21) please justify why this is the case.

C2. **Priority request**: Please provide the results of the MTC with all the luteinising hormone-releasing hormone (LHRH) agonists so that there are 3 groups within the MTC network: degarelix; LHRH agonists (including goserelin, leuprorelin and triptorelin); as well as bicalutamide monotherapy.

C3. **Priority request**: Please provide the results of the MTC for all outcomes including adverse events in the MTC. If this is not possible, please justify.

C4. Please provide full details of methods, data description and results for pooled analyses including:

- Prostate-specific antigen (PSA; page 70)
- Level of alkaline phosphatase in serum (s-ALP) (page 72)
- testosterone ≤.5mg/ml (page 74)
- summary of model results provided in Table 52 (page 190).

C5. Please clarify how the non-significant difference in overall survival (page 86) between LHRH agonists in the MTC demonstrates equivalence in clinical efficacy and effectiveness.

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C6. Please clarify why only 4-week and 12-week data were used to report PSA response results (page 7) and why 8-week data were not reported.

C7. Please clarify which methods were used to handle crossover in CS21A (page 90)? If none, please justify.

C8. Trial CS35 was deemed to be not fully applicable to the decision problem due to the use of an unlicensed dose of degarelix (page 65). However, results from CS35 are included in a pooled analysis for PSA and overall survival (and not highlighted as commercial in confidence). Conversely data from CS37 were excluded from the survival analysis on the basis of an incompatible degarelix maintenance dose (page 78). Please justify the inclusion of CS35 in these analyses.

C9. Please clarify what the timepoint was for the odds ratio in the MTC for death (page 87).

C10. For the subgroup analysis of men with pre-existing cardiovascular disease (CVD), please clarify how pre-existing CVD was defined.

C11. Please provide a rationale behind the assumption that the dose of leuprorelin does not have an effect on the efficacy and safety profile (page 102).

Section D: Clarification on cost-effectiveness data

D1. **Priority question**: The economic model is based on efficacy data from one trial even though 6 RCTs comparing degarelix to LHRH agonists were identified. Please clarify why these other 5 RCTs have not been used to inform the economic analysis.

D2. **Priority question**: Please provide results of the economic model using the estimates generated from question C1-C3 of the MTC. If this is not possible, please clarify the rationale for this. Please clarify why the MTC was not used to inform the model.

D3. **Priority question**: Please provide further justification for the exclusion of key subgroups from the NICE scope (page 32) in the model and clarify what is meant by “a sufficiently large number of patients”.

D4. **Priority question:** Please specify whether it is assumed in the economic model that all surviving patients receive every line of active treatment in the sequence. If this is the case, please provide evidence supporting this assumption.

D5. **Priority question**: Please provide additional details in the answer to 7.7.1 “Please explain reasons for any differences between modelled and observed results” on page 189. For example please explain differences between model and trial data for 1-year overall survival.

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D6. **Priority question**: Section 7.2 (page 112) states that degarelix is compared to each of the commonly used LHRH agonists in the scenario analysis but these results do not appear to be provided. Please provide results for all comparators included within the scope.

D7. **Priority question**: When the model is run with no adverse events and equal efficacy assumed for first-line treatments then predicted life years on chemotherapy and palliative care differs between degarelix and goserelin. Please describe how this error should be corrected.

D8. Please explain the reasons for the differences in total costs and QALYs between: (1) the *de novo* model included in this submission, (2) the model submitted to the All Wales Medicines Strategy Group, (3) the model submitted to the Scottish Medicines Council (4) the model in the Lu *et al* (2011) publication.

D9. Please clarify which surrogate-final relationships are used in the model (e.g., change in PSA progression leads to change in survival) and provide evidence to justify these relationships.

D10. Section 6.7.3 of the manufacturer's submission (page 85) states that 'only data from those RCTs that compared one-monthly dosing regimens were used'. Please clarify why 1-monthly dosing regimen was used as a criterion for the economic model.

D11. Please clarify the exact definition of response rate in the submission and the economic model.

D12. Please clarify whether duration of response and duration of treatment are assumed to be the same in the economic model.

D13. Please clarify why PSA response is used in first-line treatment in the economic model, but response rate is used in subsequent lines of treatment. Please specify how much of the QALY gain is due to first-line treatment.

D14. Please clarify why the European Association of Urology guidelines and NICE technology appraisal guidance 259 'Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen' studies were selected to base response on subsequent lines of treatment? Please describe how these studies were identified and selected. Please clarify how the distributions for duration of response were estimated in these studies and used in the economic model.

D15. Please justify why the algorithm published by Kontodimopoulos *et a*l for mapping the EORTC QLQ-C30 data into preference-based EQ-5D utilities was selected for use in the base case?

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D16. Please clarify whether the data used to inform the extrapolation of PSA progression used patient-level time-to-event data or aggregate time-to-event data (page 122)? If the latter, was a simple error-minimising process used or were other more sophisticated approaches (e.g., Guyot *et al*, (2012) BMC Medical Research Methodology, 12:9) used to deal with censoring?

D17. Please clarify why the cheapest available brand of goserelin (Novgos) was not used in the base case analysis?

D18. Table 6 (page 23) provides details of sales of LHRH agonists in England and Wales. Please provide full information on the source and limitations of this data source. Please explain why the brand of goserelin 'Novgos' and bicalutamide are not included within this table.

D19. The ERG believes that it is most appropriate to assume that treatment with degarelix/LHRH agonists will continue until death. Please explain why this assumption has not been used in the base case analysis. Treatment continuation until death is considered in a sensitivity analysis in page 187, please specify which treatment effect is assumed in this scenario.

D20. Please explain why the probabilistic sensitivity analysis applies uniform distributions for variables such as hazard ratios and unit costs where lognormal or gamma distributions would normally be used.

D21. Please provide the graphical representation of all curves considered for goodness of fit of the Kaplan Meier data in section 7.

D22. On page 102 it is stated that a pooled analysis concluded that the treatment effect of degarelix is not dependent on disease stage. However, on page 131 it can be read that the efficacy of degarelix is greatest in patients with metastatic disease. Please clarify and justify the rationale for these statements.

Section E: Textual clarifications and additional points

E1. The Tyrell *et* al (1998) study compares bicalutamide with castration. Page 84 states that the study uses "3.6mg goserelin" as one of the interventions compared. Please clarify where in the Tyrell (1998) paper this information is stated.

E2. The CONSORT flow chart for CS30 (page 59) states that only 11 participants completed per protocol in the goserelin group. The ERG believe the correct number for the PP cohort should be 59 – please confirm this is correct.

E3. Please clarify that the data presented in Figure 17 relates to percentage of patients and not events (page 95).

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E4. Table 24 (page 125) reports a hazard ratio of 1.71 but does not detail what hazard the values relate to. Table 32 states that 1.71 is the hazard ratio for PSA progression. The economic model ('Efficacy' sheet) states that 1.71 is the hazard ratio for response rate. Please clarify.

E5. The total QALY gain for goserelin is 5.27 in Table 55 but 5.28 in model. Please clarify.

E6. In Table 52 on page 190 the comparator is sometimes LHRH agonists and sometimes Leuprorelin. Please clarify.