NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Degarelix for treating advanced hormone-dependent prostate cancer

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Prostate Cancer Support Federation	The patients that I represent will be pleased that the committee acknowledged the rapidity with which Degarelix acts and that it does not cause a problem with a testosterone flare and has reduced cardiovascular events when compared with the agonists. I believe the patients will be disappointed that the committee have only recommended the use of this drug when a patient has impending spinal compression from metastatic disease (a relatively unusual problem) but have as yet failed to recognise its quick action to relieve pain from skeletal metastases (a more common problem) and its value in relieving impending ureteric and urethral obstruction. (Urethral obstruction from a malignant prostate may otherwise need prostatic surgery with a three or four day hospital stay, possible surgical complications and added expense.) Patients would like the committee to consider adding these indications to the guidelines for the use of this drug.	Comment noted. The Committee noted comments highlighting that degarelix is particularly beneficial compared with LHRH agonists for the subgroups of people with pre-existing cardiovascular disease, people with skeletal metastases and people with impending ureteric and urethral obstruction, and that these subgroups should be considered. The Committee noted that the manufacturer did not include any subgroup analyses and did not provide any estimate of the ICER for these subgroups. The Committee was therefore unable to consider the cost-effectiveness of degarelix compared with LHRH agonists in these subgroups (please see section 4.20 of the FAD).
Prostate Cancer UK	Prostate Cancer UK was pleased to learn that NICE are proposing to recommend the use of degarelix as an option for hormone-dependent prostate cancer, only in people with spinal metastases who are at risk of impending spinal cord compression. We believe that the Committee has taken account of the criteria as set out in the Appraisal consultation document. We hope this decision is confirmed at the Committee meeting on 11th February 2014. We would then urge the Final Appraisal Document be published as soon as possible.	Comment noted. The final draft guidance recommends degarelix as an option for treating advanced hormone-dependent prostate cancer, only in people with spinal metastases who present with signs or symptoms of impending spinal cord compression (please see section 1.1 of the FAD).
British Association of Urological Surgeons	I am writing on behalf of the British Association of Urological Surgeons, Section of Oncology. Our only comment on the ACD is that we think there should be guidance on the ongoing treatment after castrate testosterone is achieved using Degarelix - whether patients should continue Degarelix or be switched to an LHRH analogue in the interests of cost saving?	Comment noted. The Committee noted that it can only make recommendations on the technology under appraisal and within the boundaries of its marketing authorisation (please see section 4.2 of the FAD).
Ferring Pharmaceuticals	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.	Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the Evidence Review Group's (ERG) economic analysis and the manufacturers' submissions. It also carefully considered the comments received from consultees and commentators in response to the ACD.

Consultee	Comment	Response
	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	**Meta-regression** As described in section 4.19 of the FAD, the Committee noted that, as per the ERG's additional exploratory analyses, the incremental cost-effectiveness ratio (ICER) for degarelix compared with 3-monthly triptorelin was £103,200 per QALY gained when its preferred assumption of no differences in PSA progression or death, and no differences in the rate of fractures and cardiovascular adverse events between degarelix and the LHRH agonists was applied. It also noted that the ICERs for degarelix when other LHRH agonists were considered ranged from £70,600 per QALY gained compared with monthly triptorelin to £105,400 per QALY gained compared with 6-monthly triptorelin. The Committee noted that all ICERs were outside the range normally considered as a cost-effective use of NHS resources. **Subgroups of people at high risk of PSA progression and/or with pre-existing cardiovascular disease** The Committee was aware of the ERG's comments that pooled analyses should be interpreted with caution and that the manufacturer's meta-regression analyses had limitations (please see sections 3.49, 3.50 and 4.7 of the FAD). The Committee agreed with the ERG's comments and further noted that CS35 included an unlicensed dose of degarelix, the analyses were not pre-specified and were conducted post hoc. 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 (please see section 4.7 of the FAD).

Consultee	Comment	Response
		The Committee discussed in detail the clinical evidence presented for people with pre-existing cardiovascular disease and concluded that because of the uncertainty around both the pooled analyses and the meta-regression analyses presented by the manufacturer, and the lack of a robust evidence confirming the effect of degarelix on reducing the risk of cardiovascular events compared with LHRH agonists, it was not possible to conclude that degarelix would reduce the risk of cardiovascular events in people with pre-existing cardiovascular disease compared with LHRH agonists (please see section 4.10 of the FAD).
Ferring Pharmaceuticals	**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).	Comment noted. The Committee considered all the evidence submitted, including the information presented in the manufacturer's original submission and the submission of additional evidence clarifying the mechanism of action for degarelix. The Committee noted the results from the extension CS21A trial. It also noted the ERG's comment that this difference between degarelix and leuprorelin was not demonstrated in CS21A because this trial did not include a comparator arm as all patients switched from leuprorelin to degarelix. The Committee also noted the results of the manufacturer's pooled analyses together with the results of the meta-regression analyses for PSA progression-free survival (using data from CS21 and CS35). It was aware of the ERG's comments that pooled analyses should be interpreted with

Consultee	Comment	Response
		caution and that the manufacturer's meta-regression analyses had limitations (please see section 3.50 of the FAD). The Committee agreed with the ERG's comments and further noted that CS35 included an unlicensed dose of degarelix, the analyses were not pre-specified and were conducted post hoc. 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 (please see section 4.7 of the FAD). As noted in the Guide to the Single Technology Appraisal (STA) process, submission appendices are not normally given to the Appraisal Committee. Committee members may request the appendices for further information if they feel they are appropriate.
Ferring Pharmaceuticals	**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. 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 20134 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	Comment noted. A copy of the Albertsen et al (2013) paper was provided for the Committee at its second meeting on 11 February 2014 for further consideration. As outlined in section 4.10 of the FAD, the Committee noted that the results of the study by Albertsen et al. (2013) showed that there was a statistically significant reduction in the risk of having a cardiovascular event with degarelix compared with LHRH agonists in people with pre-existing cardiovascular disease. However it noted the authors' conclusion that because the analysis was post-hoc, the findings should only be interpreted as hypothesis generating and further randomised controlled trials will be needed to validate the observations and define the mechanism by which they occur. The Committee noted comments received during consultation outlining the potential benefits of degarelix compared with LHRH agonists in people with pre-

Consultee	Comment	Response
	with those from the pooled analysis and Albertsen et al 20134 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.	existing cardiovascular disease. The Committee discussed in detail the clinical evidence presented for this subgroup and concluded that because of the uncertainty around both the pooled analyses and the meta-regression analyses presented by the manufacturer, and the lack of a robust evidence confirming the effect of degarelix on reducing the risk of cardiovascular events compared with LHRH agonists, it was not possible to conclude that degarelix would reduce the risk of cardiovascular events in people with pre-existing cardiovascular disease compared with LHRH agonists (please see section 4.10 of the FAD). The ERG reviewed the meta-regression analyses and restated that including CS35 in the analyses was not appropriate because it included an unlicensed dose of degarelix. It noted that heterogeneity between the trials had not been appropriately assessed. The ERG stated that the interaction between trial and treatment had been adjusted together with several baseline covariates in the manufacturer's meta-regression analyses, and including other covariates could explain the heterogeneity in treatment across trials. The ERG considered that because CS21 and CS35 used different doses of degarelix, the random-effects model would have been more appropriate to detect clinical heterogeneity between trials (please see section 3.49 of the FAD). The Committee considered the results of the manufacturer's pooled analysis and the meta-regression analyses for cardiovascular events. It noted the ERG's comments that the meta-regression analyses resulted in a hazard ratio that was more plausible in terms of statistical significance than the results of the manufacturer's original pooled analyses, but when compared with the results of the individual trials the result was implausible. The Committee noted that the

Consultee	Comment	Response
		definition of cardiovascular disease in the manufacturer's analysis included a very broad composite outcome of several cardiovascular conditions (myocardial infarction, ischaemic cerebrovascular conditions, haemorrhagic cerebrovascular conditions, embolic and thrombotic events, and other ischaemic heart disease). It was also aware that cardiovascular events were reported as adverse events in the study, and were not independent study endpoints. The Committee discussed in detail the clinical evidence presented for this subgroup and concluded that because of the uncertainty around both the pooled analyses and the meta-regression analyses presented by the manufacturer and the lack of robust evidence confirming the effect of degarelix on reducing the risk of cardiovascular events compared with LHRH agonists, it was not possible to conclude that degarelix would reduce the risk of cardiovascular events in people with pre-existing cardiovascular disease compared with LHRH agonists (please see section 4.10 of the FAD).
Ferring Pharmaceuticals	**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	Comment noted. As outlined in section 4.7 of the FAD the Committee noted the post-hoc analyses of CS21 published by Tombal et al. (2010) showing a statistically significant difference between degarelix and leuprorelin for PSA progression or death, but when adjusted for baseline PSA levels and disease stage, this difference was no longer statistically significant (please see section 3.6 of the FAD for further details). The Committee also noted that the results from the meta-regression showed that the difference between degarelix and LHRH agonists for PSA progression-free survival for people with PSA level of more than 20 ng/ml at baseline and for people with locally advanced or metastatic prostate cancer was not statistically significant. It also noted that the ERG stated that manufacturer had already

Consultee	Comment	Response
	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).	adjusted for baseline risk. The Committee noted comments highlighting that degarelix is particularly beneficial compared with LHRH agonists for the subgroups of people with pre-existing cardiovascular disease, people with skeletal metastases and people with impending ureteric and urethral obstruction, and that these subgroups should be considered. The Committee noted that the manufacturer did not include any subgroup analyses and did not provide any estimate of the ICER for these subgroups. The Committee was therefore unable to consider the cost-effectiveness of degarelix compared with LHRH agonists in these subgroups (please see section 4.20 of the FAD).
Ferring Pharmaceuticals	**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 is included in the manufacturer's response and not reproduced here]). 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.	Comment noted. The Committee was aware of the ERG's comments that pooled analyses should be interpreted with caution and that the manufacturer's meta-regression analyses had limitations (please see sections 3.49 and 4.7 of the FAD). The Committee discussed the differences between a random-effects model and a fixed-effects model for the meta-regression analyses. It understood that although overall the point estimate would be expected to be similar in both models, the random-effects model assumes that each trial may be estimating different treatment effects so the observed variation is likely to be higher than for the fixed-effects model because it includes both the sampling error and an estimation of the heterogeneity of the trials. The fixed-effects model assumes that all trials are estimating the same treatment effect and any observed variation is simply the result of sampling error. It noted that the random-effects model gives a truer estimate of the underlying variability than the fixed-effects model when there is heterogeneity between trials. The Committee noted that the trials included in the

Consultee	Comment	Response
		meta-regression analyses differed in terms of: the doses of degarelix used (CS35 included an unlicensed dose), the inclusion criteria, the duration of follow-up, and the primary end points. The Committee accepted that because a random-effects model includes both the sampling error and an estimation of the heterogeneity of the trials, it would have been more appropriate for conducting the meta-regression analyses. The Committee agreed with the ERG's comments and further noted that the analyses were not pre-specified and were conducted post hoc. The Committee noted that there was a high degree of uncertainty around the meta-regression analyses and concluded that no difference in the clinical effectiveness and safety of degarelix in terms of PSA progression, reduction of cardiovascular events in people with pre-existing cardiovascular disease and reduction of risk of fractures could be assumed (please see sections 4.7, 4.9 and 4.10 of the FAD).
Ferring Pharmaceuticals	**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 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	Comment noted. The Committee noted the updated treatment pathway presented by the manufacturer in the submission of additional evidence in which abiraterone is positioned before docetaxel and enzalutamide is introduced before chemotherapy and abiraterone. The Committee understood that although there may be variation in clinical practice, the updated treatment pathway presented by the manufacturer is not consistent with current NICE guidance (please see section 4.2 of the FAD).

Consultee	Comment	Response
	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.	
Ferring Pharmaceuticals	**6. Additional quality of life and utility mapping activities** We note that the ACD states the use of the Kontodimopoulos et al. (2009) utility mapping algorithm as inappropriate 'The Committee considered that an alternative algorithm considered by the manufacturer, from McKenzie and van der Pol (2009), 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) 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.	Comment noted. The Committee discussed the updated utility values applied in the manufacturer's model. The Committee concluded that the use of the utility algorithm by McKenzie and van der Pol was an appropriate change to the model (please see section 4.16 of the FAD).
Ferring Pharmaceuticals	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	Comment noted. The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of degarelix, having considered evidence on the nature of advanced hormone-dependent prostate cancer and the value placed on the benefits of degarelix by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources (please see section 4.1 of the FAD).

Consultee	Comment	Response
	attending the AC meeting on the 11th February 2014, to help increase patient access to this valuable medicine in the NHS.	The Committee noted that, as per the ERG's additional exploratory analyses, the ICER for degarelix compared with 3-monthly triptorelin was £103,200 per QALY gained when its preferred assumption of no differences in PSA progression or death, and no differences in the rate of fractures and cardiovascular adverse events between degarelix and the LHRH agonists was applied. It also noted that the ICERs for degarelix when other LHRH agonists were considered ranged from £70,600 per QALY gained compared with monthly triptorelin to £105,400 per QALY gained compared with 6-monthly triptorelin. The Committee noted that all ICERs were outside the range normally considered as a cost-effective use of NHS resources and concluded that degarelix could not be recommended for treating advanced hormone-dependent prostate cancer (please see section 4.19 of the FAD).

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Prostate Cancer UK	I was pleased to be advised that NICE proposes to recommend the use of Degarelix as an option for advanced hormone-dependent prostate cancer, in men with spinal metastases, at risk of impending spinal cord compression. I believe that the Committee has taken account of the criteria as set out in the Appraisal consultation document and arrived at a decision based in a careful consideration of the available evidence. I hope that this decision will confirmed at the Committee meeting on 11th February 2014, that the Final Appraisal Document will be published as soon as possible thereafter and the treatment made available at the earliest opportunity for the men who will benefit from its effects at a critical stage in the progress of their disease.	Comment noted. The final draft guidance recommends degarelix as an option for treating advanced hormone-dependent prostate cancer, only in people with spinal metastases who present with signs or symptoms of impending spinal cord compression (please see section 1.1 of the FAD).
British Uro-Oncology Group	There are a number of comments to make which I would like to bring to the attention of the Appraisal Committee with regard to the clinical aspects and importance of the need for clinicians to have the choice of prescribing	Comment noted. **Cardiovascular disease:**

Nominating organisation	Comment	Response
	degarelix for men with advanced prostate cancer. Thank you in advance for sharing these with the Committee. There is enthusiasm to have the opportunity to prescribe degarelix amongst oncologists and urologists who treat prostate cancer. The initial ACD decision is extremely disappointing for clinicians and patients who are suffering with advanced prostate cancer. I do agree that degarelix should be the treatment of choice for men with imminent spinal cord compression as a result of prostate cancer, but I (along with many of my colleagues) believe that this is not the only advantage and that there should be a wider indication for prescribing degarelix in routine practice. I understand that the amiable data are not all Level 1 evidence and that some of the articles are looking at post hoc analyses, pooled data and subgroups. However, there are consistently strong signals from all these studies that when considered together add up to providing convincing evidence that degarelix could be a more effective drug in terms of delaying the time to a castrate resistant state and is also safer with less risk of cardiovascular events and death. For these reasons I feel that we should have the choice to prescribe the most effective drug at the initial stages of the disease, particularly if this can reduce cardiovascular disease progression – the consequences for the patient and the financial implications. The evidence from the pivotal CS21 study entitled: Efficacy and Safety of Degarelix: a 12 month, comparative, randomised, open-label, parallel-group phase III study in patients with prostate cancer, Klotz L et al. BJUI 2008, demonstrated the non inferiority of degarelix in addition to immediate biochemical and clinical effectiveness without flare or the need for any additional flare protection. Degarelix was shown to achieve immediate Helotestosterone reduction with a rapid PSA decrease and faster control of prostate cancer. The very low testosterone levels were maintained with degarelix. Degarelix was shown to be a well-tolerated alternative to LHRH agonists with a good safety profile. There was some discussion at the Appraisal Meeting regarding the fact that only 11% of men received an antiandrogen to prevent initial testosterone flare. The use of an antiandrogen does not totally block testosterone and the data comparing LHRH agonists to orchidectomy show some inconsistencies and it would appear that even when an antiandrogen is prescribed, this does	The Committee noted comments received during consultation outlining the potential benefits of degarelix compared with LHRH agonists in people with pre-existing cardiovascular disease. The Committee discussed in detail the clinical evidence presented for this subgroup and concluded that because of the uncertainty around both the pooled analyses and the meta-regression analyses presented by the manufacturer, and the lack of a robust evidence confirming the effect of degarelix on reducing the risk of cardiovascular events compared with LHRH agonists, it was not possible to conclude that degarelix would reduce the risk of cardiovascular events in people with pre-existing cardiovascular disease compared with LHRH agonists (please see section 4.10 of the FAD). **Testosterone response:** The Committee concluded that degarelix was non-inferior to LHRH agonists in suppressing testosterone levels and acknowledged that it is beneficial for avoiding testosterone flare which is particularly important in people with spinal metastases who present with signs or symptoms of spinal cord compression because of the known relationship between the testosterone flare when hormonal treatment starts and the risk of spinal cord compression (see section 4.6 of the FAD). **PSA progression in CS21 and CS21A:** As outlined in section 4.7 of the FAD, the Committee considered the results from CS21 for the PSA progression endpoint. It noted that there

Nominating organisation	Comment	Response
	not achieve total blockade of testosterone. The fact that whether an antiandrogen was administered or not with the initial injection does not prevent the ongoing testosterone miniflares and surges with subsequent injections. It is very possible that the immediate and continued superior suppression of testosterone accounts for the increased efficacy of degarelix seen in the post hoc analyses. The data from further analyses show consistent signals to suggest that degarelix is a potentially more effective choice especially for men with high risk advanced (metastatic) prostate cancer. 1. Degarelix also demonstrates a more rapid and sustained suppression of FSH than LHRH agonists (CS21) and a further reduction of FSH was demonstrated in the crossover study when men treated with leuprorelin were changed to degarelix (CS21A). FSH is thought to have an impact on prostate cancer progression and has been shown to stimulate the growth of PC3 prostate cancer cells (Ben-Josef et al. J Urol 1999;161:970–6). It has also been demonstrated that subsets of prostate cancer express FSH receptor mRNA and protein at levels higher than those of normal and hyperplastic tissues (Mariani et al. J Urol 2006;175:2072–7) and that hormone-refractory prostate cancer cells express FSH and biologically active FSH receptor (Ben-Josef et al. J Urol 1999;161:970–6). This more profound and sustained reduction of FSH with degarelix could be a further alternative theory as to why it appears to be more effective 2. Additional analysis of the Secondary Endpoint of Biochemical Recurrence Rate in a Phase III trial (CS21) Comparing Degarelix 80mg Versus Leuprolide in Prostate Cancer Patients Segmented by Baseline Characteristics, (Tombal B et al. Eur Urol 2010.) showed that degarelix reduced PSA levels more rapidly than leuprorelin, irrespective of baseline disease stage and PSA progression-free survival was significantly longer with degarelix than leuprorelin in the ITT population. Also, patients with baseline PSA >20 ng/mL were significantly less likely to experience PSA failure with degarelix in an unadjusted analysis. 3. The CS21 a (Phase III Extension Trial with a 1-arm crossover from	was a statistically significant difference between degarelix and leuprorelin for the median percentage change in PSA levels. The Committee also noted that post-hoc analyses of subgroups from CS21 showed that there was no statistically significant difference in the proportion of patients with metastatic disease who experienced PSA progression between treatment groups, and this was also similar in patients with locally advanced disease. The Committee noted the post-hoc analyses of CS21 published by Tombal et al. (2010) showing a statistically significant difference between degarelix and leuprorelin for PSA progression or death, but when adjusted for baseline PSA levels and disease stage, this difference was no longer statistically significant. The Committee noted the results from the extension CS21A trial. It also noted the ERG's comment that this difference between degarelix and leuprorelin was not demonstrated in CS21A because this trial did not include a comparator arm as all patients switched from leuprorelin to degarelix. 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 (please see section 4.7 of the FAD). The Committee noted that the results from the manufacturer's meta-regression showed that the difference between degarelix and LHRH agonists for PSA progression-free survival for people with PSA level of more than 20 ng/ml at baseline and for people with locally advanced or metastatic prostate cancer was not statistically significant. It also noted that the ERG stated that the manufacturer had already adjusted for baseline risk (please see

Nominating organisation	Comment	Response
	leuprolide to degarelix (Crawford E.D et al. J Urol 2011.) demonstrated that men switching from leuprorelin to degarelix, experienced a lower rate of PSA failure or death following an interim analysis at 27.5 months. 4. Data investigating the changes in serum alkaline phosphatase (s-ALP) levels in patients with prostate cancer receiving degarelix or leuprolide (Schroder F.H et al. BJU Int 2009) showed that greater S-ALP reductions were seen in patients with metastatic disease receiving degarelix compared with leuprorelin and that the late rises in S-ALP seen in leuprorelin patients (indicating possible therapy failure) were not observed in those receiving degarelix. These data suggest better S-ALP control and potentially longer control of skeletal metastases with degarelix. This paper had apparently not been reviewed by the committee and should be considered before a final decision is made as it could be a further signal of efficacy	section 4.7 of the FAD). **S-ALP:** Serum alkaline phosphatase level was not included as an outcome in the scope. The manufacturer presented a pooled analysis on serum alkaline phosphatase levels in its submission and the ERG considered that this analysis should be interpreted with caution because only the significant finding from a post hoc subgroup analysis of patients with metastatic disease was reported, the analysis was not defined a priori and the baseline characteristics for this subgroup were not presented (please see sections 3.9 and 3.25 of the FAD). Reference to the paper by Schroder et al. (2009) based on the results from the CS21 trial is included in both the manufacturer's submission and the ERG's report.
	Important data were submitted with regards to cardiovascular (CV) morbidity and mortality. This is a major complication for men with prostate cancer being treated with LHRH agonists and represents a great clinical and economic burden. The paper by Albertson had been made available and is to be published imminently. It is important to note that although this is a pooled analysis, all the original data from prospective studies has been independently assessed by Albertson's team. The patients in both groups were evenly matched for disease state and previous co-morbid factors. Even though this is not a randomised, prospective study, there is a strong signal of a difference and there are patients with pre-existing CV risk for whom, in light of this data, I would be more comfortable prescribing degarelix than a LHRH agonist. The conclusions from this paper were that over one year of treatment, when patients with a history of CV disease at baseline were treated with degarelix, they had a significantly lower probability of a serious CV event or death than those treated with a LHRH agonist. There was also a reduction in risk of experiencing a serious CV event of greater than 50% compared with those treated with a LHRH	A copy of the Albertsen et al. (2013) paper was provided for the Committee at its second meeting on 11 February 2014 for further consideration. As outlined in section 4.10 of the FAD, the Committee noted the results of the study by Albertsen et al. (2013) showed that there was a statistically significant reduction in the risk of having a cardiovascular event with degarelix compared with LHRH agonists in people with pre-existing cardiovascular disease. However it noted the authors' conclusion that because the analysis was post-hoc, the findings should only be interpreted as hypothesis generating and further randomised controlled trials will be needed to validate the observations and define the mechanism by which they occur.

Nominating organisation	Comment	Response
	agonist. The rationale for the differences seen in cardiovascular events in men with a pre-existing cardiovascular disease are summarised below as in the Albertson paper. The hypotheses are that the adverse effects on CV disease of LHRH agonists could be the destabilisation of established vascular lesions. Most acute cardiovascular events, including myocardial infarction and stroke, are caused by rupture of an atherosclerotic plaque. Activation of the GnRH receptors results in T cell activation including increased proliferation and expression of the IL-2 receptor degarelix as an antagonist would not have this effect. In addition GnRH antagonists suppress both LH and FSH as opposed to GnRH agonists which primarily suppress LH. FSH receptors have been found on the luminal endothelial surface of proliferating tissue and may also play a role in endothelial cell function, lipid metabolism and fat accumulation that may increase the risk of cardiovascular disease in men on LHRH agonists. These hypotheses are all supported by the observation that a GnRH antagonist is associated with a lower incidence of cardiac events only in subjects with pre-existing cardiovascular disease and that this difference becomes apparent within seven months. I do feel that these data cannot be ignored and as an Oncologist seeing over 800 new patients a year with prostate cancer, would feel it is difficult to now prescibe an agonist to men with previous cardivascular events knowing that there is an alternative that could reduce their chances of death from further cardiovascular events. This is also the opinion of many of my colleagues. In summary: I agree that degarelix should be the first therapy choice for men with risk of, or established, spinal cord compression, but feel very strongly that this should not be the only indication in view of the evidence described above. I would propose that degarelix should be available as an option for: • men with advanced (metastaic) prostate cancer who have been diagnosed with high risk disease with a PSA >20 for initiation and	The Committee considered the results of the manufacturer's pooled analysis and the meta-regression analyses for cardiovascular events. It noted the ERG's comments that the meta-regression analyses resulted in a hazard ratio that was more plausible in terms of statistical significance than the results of the manufacturer's original pooled analyses, but when compared with the results of the individual trials the result was implausible. The Committee noted that the definition of cardiovascular disease in the manufacturer's analysis included a very broad composite outcome of several cardiovascular conditions (myocardial infarction, ischaemic cerebrovascular conditions, haemorrhagic cerebrovascular conditions, embolic and thrombotic events, and other ischaemic heart disease). It was also aware that cardiovascular events were reported as adverse events in the study, and were not independent study endpoints. The Committee discussed in detail the clinical evidence presented for this subgroup and concluded that because of the uncertainty around both the pooled analyses and the meta-regression analyses presented by the manufacturer, and the lack of a robust evidence confirming the effect of degarelix on reducing the risk of cardiovascular events compared with LHRH agonists, it was not possible to conclude that degarelix would reduce the risk of cardiovascular events in people with pre-existing cardiovascular disease compared with LHRH agonists (please see section 4.10 of the FAD).

Nominating organisation	Comment	Response
	maintainence • also men with advanced (metatsatic) prostate cancer presenting with a previous cardiovascular event.	

Comments received from commentators

Commentator	Comment	Response
National Collaborating Centre for Cancer (NCC-C)	1. NCC-C fully supports the recommendation that degarelix should be used for men with newly diagnosed metastatic prostate cancer who are at risk of impending spinal cord compression. 2. NCC-C advises the committee to consider recommending a switch to an LHRH agonist after the man has been stabilised on degarelix. Please find attached published evidence that a switch from LHRH antagonist to LHRH agonist was safe and effective after 3 months treatment with the LHRH antagonist, aberalix. The use of an LHRH agonist is more convenient with 3-monthly depot preparations available. In addition the LHRH agonists goserelin, leuprorelin and triptorelin offer significant cost savings with annual drug costs of £828 to £940 ex-VAT compared with an annual maintenance cost of £1552 ex-VAT for degarelix. These men could be on therapy for a number of years.	Comment noted. The final draft guidance recommends degarelix as an option for treating advanced hormone-dependent prostate cancer, only in people with spinal metastases who present with signs or symptoms of impending spinal cord compression (please see section 1.1 of the FAD). The Committee noted comments from consultation that indicated the usefulness of having guidance for ongoing treatment with hormonal therapy once testosterone levels have been supressed to castration levels with degarelix and the possibility of switching to LHRH agonists after that in the interests of cost savings. It noted that it can only make recommendations on the technology under appraisal and within the boundaries of its marketing authorisation for treating hormone-dependent advanced prostate cancer (see FAD section 4.2).

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope:

Department of Health

Royal College of Nursing

Comments received from members of the public

Role*	Section	Comment	Response
NHS professional 1	1	I disagree entirely with the NICE conclusions; degarelix has fewer CVS risks than LHRH agonists, and my calculations suggest that the NICE recommendation in effect to continue using LHRH agonists rather than degarelix will result in some 3,500 excess CVS events per year in the UK, including heart attack and death. As a consultant cardiologist I am very interested in any possible cardiac side effects of any treatment, especially anti-cancer treatment. There have been multiple trials raising concerns over LHRH agonists, so much so that 4 eminent American medical societies (including the American Heart Association and American Cancer Society) in 2010 issued a scientific advisory greatly raising concerns about the cardiovascular risk factor side effect profile of LHRH agonists. These were most likely in those with pre-existing cardiovascular disease (about 1/3 of prostate cancer patients). This is worrying, and requires serious thought and study for prevention. The cardiovascular data on degarelix versus LHRH agonist is sufficiently compelling to believe, and adopt as the default position. If NICE do not do so, the likelihood is that patients will die needlessly.	The Committee considered the results of the manufacturer's pooled analysis and the meta-regression analyses for cardiovascular events. It noted the ERG's comments that the meta-regression analyses resulted in a hazard ratio that was more plausible in terms of statistical significance than the results of the manufacturer's original pooled analyses, but when compared with the results of the individual trials the result was implausible. The Committee noted that the definition of cardiovascular disease in the manufacturer's analysis included a very broad composite outcome of several cardiovascular conditions (myocardial infarction, ischaemic cerebrovascular conditions, haemorrhagic cerebrovascular conditions, embolic and thrombotic events, and other ischaemic heart disease). It was also aware that cardiovascular events were reported as adverse events in the study, and were not independent study endpoints (please see section 4.10 of the FAD). The Committee also noted the results of a study by Albertsen et al. (2013). The Committee was mindful that Albertsen et al. concluded that the study has several limitations, the findings should only be interpreted as hypothesis generating and that

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
			randomised controlled trials will be needed to validate the observations and define the mechanism by which they occur. The Committee discussed in detail the clinical evidence presented for this subgroup and concluded that because of the uncertainty around both the pooled analyses and the meta-regression analyses presented by the manufacturer, and the lack of a robust evidence confirming the effect of degarelix on reducing the risk of cardiovascular events compared with LHRH agonists, it was not possible to conclude that degarelix would reduce the risk of cardiovascular events in people with pre-existing cardiovascular disease compared with LHRH agonists (please see section 4.10 of the FAD).
	2	The finding in 1941 that prostate cancer is a hormone dependent cancer (testosterone) led to Huggins receiving the Nobel prize in 1966. This was a key advance in the management of prostate cancer and led to an understanding that testosterone removal/receptor blockade was vital to the successful management of this condition. A drug such as degarelix that immediately and massively lowers testosterone levels is scientifically very attractive. Conversely, any drug that increases testosterone levels must be avoided at all costs. It is therefore bizarre in the extreme that the LHRH agonists, which produce a massive surge of testosterone at initiation, only partially blocked by testosterone antagonists given by some oncologists some of the time, are in any sense a recommended therapy. Intellectually, using GnRH antagonists to block testosterone production is an elegant way of lowering testosterone levels, and does so without producing a tumour enhancing hormone flair. This is particularly the case as we know that any testosterone receptor blocking drug is only partially effective, and can in no way fully counteract the tumour enhancing testosterone flair resulting from LHRH agonists.	The Committee concluded that degarelix was non-inferior to LHRH agonists in suppressing testosterone levels and acknowledged that it is beneficial for avoiding testosterone flare which is particularly important in people with spinal metastases who present with signs or symptoms of spinal cord compression because of the known relationship between the testosterone flare when hormonal treatment starts and the risk of spinal cord compression (please see section 4.6 of the FAD).

Role*	Section	Comment	Response
	3	As a cardiologist I am interested in CVS risk generally, and particular in cancer and its treatment. Prostate cancer is particularly relevant as patients are already at high risk of CVS events (men, elderly), and some 1/3 have pre-existing CVS disease. Anything that increases risk, even if marginally, given the high pre-existing risk will be very detrimental. There is a strong steer from the data that LHRH agonists increase CVS risks, especially in those with pre-existing CVS disease. The risk is about 60% lower with degarelix, according to the data of Bertrand Tombal et al. Put another way, in those with CVS disease the risk of a serious CVS event at 1 year on LHRH agonists is about 12%, with degarelix 5%, an absolute risk difference of 7%. With some 150,000 patients receiving LHRH agonists in the UK, and 1/3 with CVS disease, there will be (50,000 x 0.07) about 3,500 fewer serious CVS event will occur if degarelix is used rather than the inelegant LHRH agonists.	Please see response in section 1 above.
	4	I cannot see the rationale for NICE supporting a drug that increases testosterone levels at a mission critical stage of a hormone responsive illness. NICE have failed to present evidence that testosterone receptor blockers are used universally, or are 100% effective. There is accumulating evidence that the testosterone flair may translate into LHRH agonists being less effective anti-cancer drugs than the GnRH antagonist degarelix. NICE also has not produced evidence that patients are fully informed about the LHRH testosterone flair. Finally, as a cardiologist, I am very impressed with the power of the pooled analysis by Bertrand Tombal et al that degarelix has fewer CVS side effects than LHRH agonists. NICE may not like pooled analyses, but we live in an imperfect world; the data is good, and we should go with this. If NICE gets this wrong, there will be 35,000 patients (at 10 years) with unnecessary heart attacks and CVS death. If degarelix were more expensive than the alternatives, then one could titrate cost against gain; my understanding is that there is no difference in cost, and NICE is therefore compelled to go with the drug with the safer side effect profile.	The Committee noted that it can only make recommendations on the technology under appraisal and within the boundaries of its marketing authorisation for treating hormone-dependent advanced prostate cancer (see FAD section 4.2). It cannot make recommendations on the comparator technologies. Please see response in section 1 regarding the Committee's conclusions on cardiovascular events.

Role*	Section	Comment	Response
	5	Patients must be given choice in their health care treatments, particularly for emotive diseases such as cancer. For choice to mean anything patients must be informed of the therapeutic benefit and side effect profile of alternative treatments. Patients must be informed of the testosterone flair with LHRH agonists (and that fact that prostate cancer is stimulated by testosterone) and the risks of this. They should be offered a drug without a flair, if choice in the NHS is to mean anything at all. Furthermore, patients with CVS disease must be told of the highly suggestive data informing us that degarelix has less CVS risk than LHRH agonists. If choice matters, then NICE must support this and support degarelix. If they do not, then NICE have clearly positioned themselves as not supporting patient choice, and by extension, if you have no choice over your treatment, then there is no role for patient education in prostate cancer. This would be a sad day, it would position NICE as an organisation which might pay lip service to modernity in the NHS, but which is essentially old fashioned authoritarian and paternalistic.	Comment noted. Although individual choice is important for the NHS and its users, they should not have the consequence of promoting the use of interventions that are not clinically and/or cost effective" (Social Value Judgements - Principles for the development of NICE guidance; principle 5). The Committee concluded that degarelix was non-inferior to LHRH agonists in suppressing testosterone levels and acknowledged that it is beneficial for avoiding testosterone flare which is particularly important in people with spinal metastases who present with signs or symptoms of spinal cord compression because of the known relationship between the testosterone flare when hormonal treatment starts and the risk of spinal cord compression (please see section 4.6 of the FAD). The Committee noted that the ICER for degarelix compared with 3-monthly triptorelin was £103,200 per QALY gained when its preferred assumption of no differences in PSA progression or death, and no differences in the rate of fractures and cardiovascular adverse events between degarelix and the LHRH agonists was applied. It also noted that the ICERs for degarelix when other LHRH agonists were considered ranged from £70,600 per QALY gained compared with monthly triptorelin to £105,400 per QALY gained compared with 6-monthly triptorelin. The Committee noted that all ICERs were outside the range normally considered as a cost-effective use of NHS resources and concluded that degarelix could not be recommended for treating advanced hormone-dependent prostate cancer (please see section 4.19 of the FAD). Please see the response in section 1 above regarding the Committee's conclusions on cardiovascular events.

Role*	Section	Comment	Response
NHS professional 2	1	There is a problem with recommendation 1.1. I would really want to start treatment on a man with a very high PSA when I first met him. I would not wait for bone or other scans. Men with a very high PSA should be considered for degarelix immediately, not after MR or bone scans show impending spinal cord compression. In addition, patients presenting with renal failure due to ureteric compression should be eligible	As outlined in section 3.50 of the FAD, the ERG noted that for PSA progression-free survival, although the adjusted hazard ratio from the meta-regression analyses was statistically significant for degarelix compared with LHRH agonists in the overall population, it was not statistically significant for people with PSA of more than 20 ng/ml at baseline and for people with locally advanced or metastatic disease. The Committee noted that the ERG stated that the manufacturer had already adjusted for baseline risk (please see section 4.7 of the FAD). The Committee noted comments highlighting that degarelix is particularly beneficial compared with LHRH agonists for the subgroups of people with pre-existing cardiovascular disease, people with skeletal metastases and people with impending ureteric and urethral obstruction, and that these subgroups should be considered. The Committee noted that the manufacturer did not include any subgroup analyses and did not provide any estimate of the ICER for these subgroups. The Committee was therefore unable to consider the cost-effectiveness of degarelix compared with LHRH agonists in these subgroups (see FAD section 4.20).
	2	I am not sure why the ERG feel that cardiovascular events would be the same in degarelix and LHRH treated patients. I appreciate that the differences in cardiovascular events was shown in a post hoc analysis of pooled data, which is not ideal, but, on a balance of probability, it is extremely likely that cardiovascular risk is lower in degarelix treated patients.	Comment noted. The Committee considered the results of the manufacturer's pooled analysis and the meta-regression analyses for cardiovascular events. It noted the ERG's comments that the meta-regression analyses resulted in a hazard ratio that was more plausible in terms of statistical significance than the results of the manufacturer's original pooled analyses, but when compared with the results of the individual trials the result was implausible. The Committee noted that the definition of cardiovascular disease in the manufacturer's analysis included a very broad

Role*	Section	Comment	Response
			composite outcome of several cardiovascular conditions (myocardial infarction, ischaemic cerebrovascular conditions, haemorrhagic cerebrovascular conditions, embolic and thrombotic events, and other ischaemic heart disease). It was also aware that cardiovascular events were reported as adverse events in the study, and were not independent study endpoints. The Committee also noted the results of a study by Albertsen et al. (2013). The Committee was mindful that Albertsen et al. concluded that the study has several limitations, the findings should only be interpreted as hypothesis generating and that randomised controlled trials will be needed to validate the observations and define the mechanism by which they occur. The Committee discussed in detail the clinical evidence presented for this subgroup and concluded that because of the uncertainty around both the pooled analyses and the meta-regression analyses presented by the manufacturer, and the lack of a robust evidence confirming the effect of degarelix on reducing the risk of cardiovascular events compared with LHRH agonists, it was not possible to conclude that degarelix would reduce the risk of cardiovascular events in people with pre-existing cardiovascular disease compared with LHRH agonists (please see section 4.10 of the FAD).
NHS professional 3	1	There are other patients who would benefit for this medication not just spinal mets. Patients with bone pain (in other areas) benefit and are often pain free 10 days after starting this treatment. Patients with high disease burden (e.g. very high PSA) benefit. Patients with post renal failure/hydronephrosis benefit as this is often relieved after starting this treatment. Patients with significant cardiac co-morbidities have been shown to	Comment noted. The Committee noted that the results from the manufacturer's meta-regression analyses showed that the difference between degarelix and LHRH agonists for PSA progression-free survival for people with PSA level of more than 20 ng/ml at baseline and for people with locally advanced or metastatic prostate cancer was not statistically significant. It also noted that the ERG stated that the manufacturer had already adjusted

Role*	Section	Comment	Response
		benefit. I believe restricting this medicine to 'only spinal mets' is wrong	for baseline risk (please see section 4.7 of the FAD). The Committee discussed in detail the clinical evidence presented for the subgroup of people with pre-existing cardiovascular disease and concluded that because of the uncertainty around both the pooled analyses and the meta-regression analyses presented by the manufacturer, and the lack of a robust evidence confirming the effect of degarelix on reducing the risk of cardiovascular events compared with LHRH agonists, it was not possible to conclude that degarelix would reduce the risk of cardiovascular events in people with pre-existing cardiovascular disease compared with LHRH agonists (please see section 4.10 of the FAD). The Committee noted comments highlighting that degarelix is particularly beneficial compared with LHRH agonists for the subgroups of people with pre-existing cardiovascular disease, people with skeletal metastases and people with impending ureteric and urethral obstruction, and that these subgroups should be considered. The Committee noted that the manufacturer did not include any subgroup analyses and did not provide any estimate of the ICER for these subgroups. The Committee was therefore unable to consider the cost-effectiveness of degarelix compared with LHRH agonists in these subgroups (please see section 4.20 of the FAD).

Role*	Section	Comment	Response
	8	No oncology or urology representative	Comment noted. NICE encourages all consultees and commentators to nominate clinical specialists and patient experts to take part in the first Appraisal Committee meeting discussions. They are also invited to comment on the ACD. The Chair of the Appraisal Committee, NICE's project team and PIP team selected two consultant clinical oncologists, and two patient experts to give personal views on degarelix at the initial Committee discussion. Written evidence was also provided (please see section 10 of the FAD).