NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Degarelix for treating advanced hormone-dependent prostate cancer

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using degarelix in the NHS in England. The Appraisal Committee has considered the evidence submitted and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 9) and the public. This document should be read along with the evidence base (the Committee papers).

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using degarelix in the NHS in England.

For further details, see the Guides to the technology appraisal process.

The key dates for this appraisal are:

Closing date for comments: 26 June 2015

Next Appraisal Committee meeting: 4 August 2015

Details of membership of the Appraisal Committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9.

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1 Appraisal Committee's preliminary recommendations

1.1 Degarelix is not recommended within its marketing authorisation for treating advanced hormone-dependent prostate cancer.

1.2 People whose treatment with degarelix was started within the NHS before this guidance was published should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Degarelix (Firmagon, Ferring Pharmaceuticals) is a selective gonadotrophin-releasing hormone antagonist that reduces the release of gonadotrophins by the pituitary, which in turn reduces the secretion of testosterone by the testes. Gonadotrophin-releasing hormone is also known as luteinising hormone-releasing hormone. Because gonadotrophin-releasing hormone antagonists do not produce a rise in hormone levels at the start of treatment, there is no initial testosterone surge or tumour stimulation, and therefore no potential for symptomatic flares. Degarelix has a marketing authorisation in the UK for the 'treatment of adult male patients with advanced hormone-dependent prostate cancer'. It is administered as a subcutaneous injection.

2.2 The most common adverse reactions with degarelix are related to the effects of testosterone suppression, including hot flushes and weight increase, or injection site reactions (such as pain and

erythema). For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The starting dose of degarelix is 240 mg administered as 2 subcutaneous injections of 120 mg each, and the monthly maintenance dose is 80 mg administered as 1 subcutaneous injection. The cost of 2×120-mg vials is £260.00 and an 80-mg vial is £129.37 (excluding VAT; British national formulary May 2015). The company's estimate of a total course of treatment (including administration) is £12,306. The company estimated that, assuming treatment with degarelix continues until disease progression, the total time spent on treatment is 5.9 years (including time spent having combined androgen blockade and anti-androgen withdrawal). Costs will increase to approximately £14,800 assuming treatment with degarelix continues until death (including administration and anti-androgen withdrawal). Costs may vary in different settings because of negotiated procurement discounts.

3 The company's submission

The Appraisal Committee (section 8) considered evidence submitted by Ferring Pharmaceuticals and a review of this submission by the Evidence Review Group (ERG; section 9).

3.1 The company's submission presented evidence on the clinical effectiveness of degarelix from 6 randomised controlled trials. The main clinical trial (CS21 [n=610]) compared degarelix with leuprorelin with or without concomitant bicalutamide. Four trials compared degarelix with goserelin with or without concomitant bicalutamide (CS28 [n=42]; CS30 [n=246]; CS31 [n=182]; CS35 [n=859]), and 1 trial compared intermittent administration of degarelix with continuous administration of degarelix and continuous administration of leuprorelin (CS37 [n=409]). All the

trials were open label, done in the USA and Europe and were primarily designed to demonstrate that degarelix was non-inferior to luteinising hormone-releasing hormone (LHRH) agonists (that is, no worse than LHRH agonists) for treating hormone-dependent prostate cancer. Patients having LHRH agonists in the 6 trials also had treatment with short-term bicalutamide for flare protection, but this proportion was only 11% and 13.5% in CS21 and CS35 respectively. The proportion of patients with either locally advanced or metastatic prostate cancer ranged from 5.5% in CS37 to 60% in CS31.

3.2 The primary outcome measures in the 6 trials were: suppression of serum testosterone levels to 0.5 ng/ml or less (castration levels) between days 28 and 364 in CS21 and CS35; reduction of prostate volume (measured by transrectal ultrasound) at 12 weeks in CS30 and CS31; change in the IPSS (International Prostate Symptom Score) at 12 weeks in CS28; prostate-specific antigen (PSA) suppression (PSA levels of 4 ng/ml or less) at 14 months in CS37. Secondary outcomes in the trials included: overall survival, progression-free survival, health-related quality of life, adverse events (defined as any medical occurrence in a patient who had the investigational drug that did not necessarily have a causal relationship with the study treatment) and adverse drug reactions (defined as an adverse event rated by the investigator and/or the sponsor company as probably or possibly related to treatment with the investigational drug).

3.3 The results of CS21 demonstrated that for the primary outcome of testosterone suppression, on day 3 of the study 96.1% of patients (199 of 207) in the degarelix group had testosterone levels of 0.5 ng/ml or less compared with none in the leuprorelin 7.5 mg group ($p<0.0001$). Only 0.2% (1 of 202) of patients having the unlicensed dose of degarelix (240/160 mg) had a testosterone

increase during the first 2 weeks of treatment, compared with 80.1% (161 of 201) of patients having leuprorelin ($p<0.0001$).The company stated that degarelix showed a rapid suppression of testosterone levels that indicated a rapid onset of action and rapid disease control. The Kaplan–Meier estimates of the difference in cumulative probability of achieving testosterone levels of 0.5 ng/ml or less from days 28 to 364 in the intention-to-treat population was 0.9% (95% confidence interval [CI] -3.2% to 5.0%) for degarelix (97.2% [95% CI 93.5% to 98.8%]) compared with leuprorelin (96.4% [95% CI 92.5% to 98.2%]). The company concluded that the licensed dose of degarelix (240/80 mg) showed non-inferiority compared with leuprorelin given that the entire 2-sided (multiplicity-adjusted) 97.5% CI was greater than the non-inferiority limit of -10.0 percentage points. The company noted that in CS35 the cumulative probability of achieving testosterone levels of 0.5 ng/ml or less from days 28 to 364 was higher in the goserelin group (96.7% [95% CI 93.7% to 98.2%]) compared with the degarelix group (90.0% [95% CI 87.0% to 92.3%]) resulting in a difference of -6.7% (95% CI -10.1% to -3.3%). The company stated that this study was part of the development programme for degarelix and used an unlicensed dose of degarelix. Therefore, the study was not fully applicable to the decision problem. The company combined the estimated cumulative probabilities of achieving testosterone levels of 0.5 ng/ml or less from 4 trials (CS21; CS28; CS30; CS31) in a pooled analysis and concluded that the results were consistent with the findings from CS21, indicating that a monthly maintenance regimen of degarelix is non-inferior to LHRH agonist therapy in reducing serum testosterone levels.

3.4 In the main trial (CS21), PSA progression was defined as 2 consecutive increases in PSA levels of 50% or more and increases of more than 5 ng/ml compared with the lowest level

observed. The company stated that PSA progression is used routinely in clinical practice as a prognostic indicator to assess disease progression and treatment response. The Kaplan–Meier estimates of the probability of completing the study without PSA progression on day 364 were 91.1% (95% CI 85.9% to 94.5%) for patients having the licensed dose of degarelix (240/80 mg), 85.8% (95% CI 79.8% to 90.1%) for patients having the unlicensed dose of degarelix (240/160 mg) and 85.9% (95% CI 79.9% to 90.2%) for patients having leuprorelin. The company also presented data on the median percentage change in PSA levels from baseline to different time points in CS21, CS28, CS30, CS31 and CS35. The company stated that in CS21 the difference in the median change in PSA levels for degarelix compared with leuprorelin was statistically significant on days 14 and 28 ($p<0.0001$) indicating that degarelix showed more rapid PSA control than leuprorelin.

3.5 The company did 2 post-hoc exploratory subgroup analyses of PSA progression from CS21: PSA progression depending on the stage of the disease and PSA progression for patients with PSA levels of more than 20 ng/ml at baseline. The analyses showed that PSA progression occurred more frequently in patients with advanced prostate cancer and in patients with PSA levels of more than 20 ng/ml at baseline. There was no statistically significant difference between treatment groups in the proportion of patients with metastatic disease who had PSA progression (21.6% and 36.2% in the degarelix and leuprorelin groups respectively, $p=0.156$) and this difference was small for patients with locally advanced prostate cancer (10.9% and 11.5% in the degarelix and leuprorelin groups, respectively, had PSA progression; p value not reported). The difference between treatment groups in the proportion of patients who had PSA progression was statistically significant in patients with baseline PSA levels of 20 ng/ml or more

(16.0% of 100 patients in the degarelix group and 28.0% of 93 patients in the leuprorelin group, p=0.04).

3.6 The company presented a post-hoc analysis of the risk of progression-free survival (PSA progression or death) from CS21, published by Tombal et al. (2010). PSA progression occurred more frequently in patients having leuprorelin (12.9%) compared with degarelix (7.7%; see section 3.5). The probability of completing the study without dying was 97.4% (95% CI 93.8% to 98.9%) for degarelix and 95.1% (95% CI 90.7% to 97.4%) for leuprorelin. These results showed that patients having degarelix had a lower risk of PSA progression or death compared with patients having leuprorelin (p=0.05). When adjusted for baseline PSA levels and disease stage the results were not statistically significant (hazard ratio [HR] 0.664 [95% CI 0.385 to 1.146]). The company also reported results for disease progression (defined as PSA progression, death from any cause or the introduction of additional therapy, whichever occurred first) from CS35 and CS37. There were no statistically significant differences between degarelix and LHRH agonists for disease progression in CS37 or CS35.

3.7 The results for overall survival from CS21 showed that 2% of patients (5 of 207) and 4% of patients (9 of 201) died in the degarelix and leuprorelin groups respectively. The risk of death was 2.6% (95% CI 1.1% to 6.2%) for patients having degarelix and 4.9% (95% CI 2.6% to 9.3%) for patients having leuprorelin. The company also presented the number of deaths for each individual trial, but noted that the trials were not powered to detect statistical significance for this outcome and, because of the short duration of follow-up, the number of deaths was low.

3.8 The company included results from CS21A, the extension trial of CS21, in which all patients who had previously had leuprorelin were

randomised to 1 of the 2 degarelix groups (160 mg or 80 mg maintenance dose) and were followed up for 5 years. After a protocol amendment, all patients had a monthly degarelix maintenance dose of 80 mg. The company stated that there was sustained suppression of both testosterone and PSA levels with degarelix irrespective of whether patients had degarelix or leuprorelin during CS21. There were no statistically significant differences in the number of patients with PSA progression or testosterone suppression between the treatment groups after switching from leuprorelin to degarelix. The hazard rate of PSA progression-free survival decreased significantly after the switch in the leuprorelin group whereas the rate in those who continued on degarelix was consistent with the rate observed in CS21.

3.9 The company presented data on serum alkaline phosphatase levels from CS21. The results from the post-hoc analysis showed that, overall, the difference in serum alkaline phosphatase level suppression in patients with metastatic prostate cancer was statistically significant between degarelix and leuprorelin at day 364 (p=0.014). The company also presented a pooled analysis on serum alkaline phosphatase levels including data from CS21, CS28, CS30, CS31, CS35 and CS37. It concluded that serum alkaline phosphatase levels in patients with metastatic disease were suppressed to a greater extent over 1 year of treatment with degarelix than with leuprorelin (p=0.0383).

3.10 The company presented data for health-related quality of life, which was assessed using different measures and questionnaires in each of the 6 randomised controlled trials. In CS21, quality of life was evaluated using the SF12 v2 (Short Form 12 version 2) and the EORTC QLCQ-C30 (European Organization for Research and Treatment of Cancer, quality of life questionnaire-C 30) questionnaires to obtain generic and cancer-specific measures of

quality of life, respectively. The company stated that all the SF12 v2 scores were comparable across treatment groups and study visits and the EORTC QLQ-C30 scores were stable with no changes from baseline in median scores at any time point in the study.

3.11 The company did meta-analyses using random-effects models for the following end points: testosterone suppression, prostate size reduction, IPSS, PSA response (defined as absolute changes in PSA levels from baseline and/or PSA progression) and overall survival. For the end points of cumulative probability of testosterone levels of 0.5 ng/ml or less and differences in the percentage change in PSA levels, the company included data from CS21, CS28, CS30, CS31 and CS35. The results of the company's meta-analyses for these 2 end points showed that there was statistically significant heterogeneity between trials for the difference in the percentage change in PSA levels (based on I-squared estimates of 90.0% at week 4, 91.0% at week 8 and 81.4% at week 12) and for the difference in the cumulative probability of testosterone levels of 0.5 ng/ml or less (based on I-squared estimates of 72.8% from day 28 to 84 and 91.6% from day 28 to 364). The company suggested that heterogeneity in PSA response could be because of different baseline PSA levels resulting from the use of different eligibility criteria in the trials. For the end points of percentage change in prostate volume and change in IPSS the company included data from CS21, CS28, CS30 and CS31. For the end point of percentage change in prostate volume, the weighted mean difference between degarelix and LHRH agonists was -0.57 (95% CI -5.02 to 3.87). The company stated that this result indicated that degarelix was non-inferior to leuprorelin or goserelin plus bicalutamide. For the change in IPSS, the mean differences between degarelix and LHRH agonists were: -0.48 (95% CI -1.43 to 0.47; p=0.323) at week 4, -0.64 (-1.63 to 0.36, p=0.212) at

week 8 and -1.43 (-2.47 to -0.39, p=0.007) at week 12. The company also presented the results of the meta-analysis for overall survival from CS21, CS28, CS30, CS31 and CS35. The results showed that the mortality risk was lower in the group having degarelix compared with the group having LHRH agonists (weighted odds ratio [OR]: 0.48, 95% CI 0.25 to 0.91, p=0.025).

3.12 The company also presented pooled analyses of individual patient-level data from the 6 randomised controlled trials for the rate of adverse events, which included cardiovascular events, joint-related signs and symptoms, fractures, and urinary tract adverse events. The company pooled data from 2328 patients: 1491 had degarelix and 837 had LHRH agonists (458 had goserelin, 379 had leuprorelin). Among the patients with pre-existing cardiovascular disease, the risk of cardiac events within 1 year of starting therapy was lower for patients having degarelix compared with those having LHRH agonists (HR 0.44, 95% CI 0.26 to 0.75, p=0.0023). The probability of joint-related signs and symptoms, fractures and urinary tract adverse events was statistically significantly lower for patients having degarelix compared with patients having LHRH agonists (5.3% compared with 8.1%, p=0.0116 for joint-related signs and symptoms; 0.9% compared with 2.3%, p=0.0234 for fractures; and 15.0% compared with 22.3%, p<0.0001 for urinary tract adverse events). The company also referred to a study by Albertsen et al. (2013), which presented results of the pooled analysis for patients with pre-existing cardiovascular disease. The authors of the study concluded that, because of several limitations, the findings should only be interpreted as hypothesis-generating. They added that randomised controlled trials are needed to validate the observations and define the mechanism by which they occur.

3.13 The company did a mixed treatment comparison to explore whether the results were consistent with published meta-analyses showing

similar clinical efficacy between LHRH agonists and to determine whether there was evidence comparing degarelix with bicalutamide monotherapy. The company only included the randomised controlled trials that used the licensed dose of degarelix (240/80 mg) and compared 1-monthly dosing regimens (CS21, CS28, CS30 and CS31). The company stated that it only included overall survival in the mixed treatment comparison because of lack of data on other outcomes. It presented the results in terms of odds ratios (OR). The results favoured degarelix compared with leuprorelin (OR 1.765) and goserelin (OR 1.549), but not when compared with triptorelin (OR 0.505). None of these results was statistically significant. The company stated that the lack of evidence to compare bicalutamide with degarelix prevented a robust comparison and that a naive indirect comparison was not done because it could provide misleading or biased estimates of treatment effects.

3.14 The company's submission included a de novo economic analysis that assessed the cost effectiveness of degarelix compared with goserelin plus short-term anti-androgen treatment with bicalutamide for treating advanced hormone-dependent prostate cancer. The company stated that goserelin was chosen as the comparator for its base-case analysis because it is the most commonly prescribed LHRH agonist in England and Wales. It also included comparisons between degarelix and other LHRH agonists (leuprorelin and triptorelin plus short-term anti-androgen treatment with bicalutamide) in scenario analyses. The company stated that given the lack of clinical evidence comparing degarelix with bicalutamide monotherapy, it did not include this comparison in the model. The model was a treatment sequence Markov model with 7 states: first-line treatment for hormone-dependent prostate cancer, anti-androgen addition, anti-androgen withdrawal, first-line

chemotherapy with docetaxel for hormone-refractory prostate cancer, abiraterone, supportive and palliative care, and death. All patients followed an identical treatment pathway in the model and had each treatment if they were still alive. The model had a cycle length of 4 weeks (28 days) and a lifetime time horizon of 30 years. The cost-effectiveness analysis was conducted from a NHS perspective, costs and outcomes were discounted at 3.5% per year.

3.15 The company assumed that the efficacy and safety profiles of triptorelin and goserelin were equivalent to those of leuprorelin (the comparator in CS21), but chose goserelin as the comparator for the base-case analysis. The clinical inputs in the model were based on the intention-to-treat population from CS21 and CS21A. The company also did a subgroup analysis of patients with PSA levels greater than 20 ng/ml in CS21 because it suggested that these patients better reflected the population having hormonal therapy in the UK.

3.16 The company made the following assumptions in the base-case analysis:

- differential efficacy between treatment groups continued after the trial period of 1 year
- efficacy across the different doses of LHRH agonists was equivalent
- patients who initially had mild spinal cord compression that improved had the same utility as those whose spinal cord compression resolved completely
- patients with metastatic disease that progressed on first-line treatment had an increased risk of mortality

- patients who had a non-fatal cardiovascular event did not experience an additional utility decrement from 28 days after the event
- rates of adverse events were not dependent on the dose of degarelix given, based on the data from the 6 pooled trials that included different doses and regimens of degarelix.

3.17 All patients in the model started on first-line treatment with degarelix or LHRH agonists. Patients moved through the model to have subsequent treatments depending on PSA progression. The company stated that, based on expert opinion, PSA progression was a good indicator of biochemical disease progression. The treatment effect of degarelix was derived from the Kaplan–Meier probability estimates from CS21 and CS21A. The company investigated the fit of different parametric curves to the Kaplan–Meier data for patients having degarelix and concluded that the log-normal distribution proved the best fit for both the intention-to-treat population and the high-risk population of patients with PSA greater than 20 ng/ml. The company applied the 1-year treatment effect observed in CS21 to the parametric curves, assuming proportional hazards. It also explored the sensitivity of the model results to the proportional hazards assumptions in a sensitivity analysis.

3.18 The company modelled patient progression through subsequent treatments based on mean duration of response; response rates to anti-androgen addition, anti-androgen withdrawal and docetaxel were based on estimated response durations reported in the European Association of Urology guidelines. Mean duration of response to treatment with abiraterone was derived from NICE's technology appraisal guidance on abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen. It was assumed that after anti-androgen withdrawal, all patients would have metastatic disease.

3.19 The survival data used to determine transition probabilities for patients moving to the death state were derived from age-specific mortality rates from the Office of National Statistics and adjusted using prostate cancer age-specific survival data from the Scottish Cancer Registry. The company selected a log-logistic distribution to extrapolate additional mortality above the rate that would be expected for the general population because this produced the lowest mean absolute error compared with the observed data. The company generated separate survival curves for patients with metastatic disease and those with non-metastatic disease. In the model patients faced different risks of mortality as they progressed through each treatment. The company applied a weighted survival to patients on first-line treatment with degarelix or LHRH agonists based on the proportion of patients who had localised, locally advanced and metastatic disease in CS21. The company assumed in the model that there was a link between progression on first-line treatment (based on PSA progression) and an increased risk of mortality for patients with metastatic disease. Assuming that there was a link, delayed progression from the first-line treatment states resulted in a lower mortality risk. This assumption was supported by Hussain et al. (2009), who showed that PSA progression, defined as an increase of 25% or more over the lowest PSA level and an absolute increase of 2 or 5 ng/ml or more, predicted overall survival. The company stated that using data from CS21 overestimated the proportion of patients with localised disease. This would underestimate the benefit from degarelix in the intention-to-treat population because the trial results suggested that the efficacy of degarelix was greatest in patients with metastatic disease. The company applied a reduced mortality risk to patients with metastatic disease having abiraterone based on NICE technology appraisal guidance on abiraterone for castration-resistant metastatic prostate cancer previously treated with a

docetaxel-containing regimen. It also assumed a reduced mortality risk for patients having degarelix who had a cardiovascular event because this risk was assumed to have already been captured in the relative prostate cancer mortality rates, based on the assumed lower risk of cardiovascular events with degarelix compared with LHRH agonists.

3.20 The company incorporated the rate of adverse events in the model and assumed that patients having degarelix and LHRH agonists could have fractures, joint-related signs and symptoms and cardiovascular events. In contrast, only patients having LHRH agonists could have spinal cord compression because it was assumed that this was a result of the testosterone flare associated with LHRH agonists. The company modelled musculoskeletal and cardiovascular events using parametric curves fitted to the pooled observations of the 6 randomised controlled trials included as clinical evidence. The company estimated that the hazard of having a joint-related signs and symptoms event decreased over time for both treatment groups and the hazard of having a fracture decreased over time for degarelix but increased for the LHRH agonists. The company applied long-term quality-of-life and cost decrements for patients who remained in pain from severe joint-related signs and symptoms and severe fractures based on the proportion of patients remaining in pain for each cycle. The company derived the risk of having spinal cord compression from the economic evaluation by Lu et al. (2011) based on the data from Oh et al. (2010) and assumed that the mortality risk for patients with spinal cord compression was similar to the mortality risk for the rest of the patient population in the model. The company only applied the risk of having a cardiovascular event to those patients who had a cardiovascular event at baseline (30.7% of patients), because the pooled trial data only indicated a statistically significant

difference between degarelix and leuprorelin for these patients. It used separate curves to account for fatal and non-fatal events and assumed that patients who had a cardiovascular event would have treatment for this condition until death. The company did not incorporate the incidence of any other adverse events in the model.

3.21 Utility values in the model were obtained from health-related quality-of-life data from CS21 and studies identified in the literature review. The literature indicated that, as patients progressed to subsequent treatments, their health-related quality of life decreased. The company applied different mapping algorithms (the algorithm from the Health Economics Research Centre based on Gray et al. [2004], and the algorithms from Kontodimopoulos et al. [2009] and McKenzie and van der Pol [2009]) to transform health-related quality-of-life data from CS21 into utility values based on the EQ-5D questionnaire. The company selected the utility values obtained with the mapping algorithm by Kontodimopoulos et al. when possible in the economic analysis because this algorithm was derived from patients with a less severe condition, comparable to that of the patients with advanced hormone-dependent prostate cancer in CS21. The difference in utility values between treatment groups was not statistically significant (p=0.27) when using the Kontodimopoulos et al. algorithm. Utility decrements associated with joint-related signs and symptoms, fractures and cardiovascular events were also applied in the model using the Kontodimopoulos et al. algorithm. Utility decrements associated with spinal cord compression were based on Lu et al (2011). The company did sensitivity analyses to determine how robust the results of the model were to the utility values obtained using other mapping algorithms and other sources of utility values identified in the systematic review. This variation did not have a big impact on the cost-effectiveness results.

3.22 The company also did a systematic review to identify cost and resource use studies in patients with advanced prostate cancer. Drug costs were taken from public sources (the British national formulary [BNF] edition 65 and Commercial Medicines Unit – Electronic Marketing Information tool [eMIT]). The company assumed that the unit costs for the monthly dose of leuprorelin (Prostap), goserelin (Zoladex) and triptorelin (Decapeptyl) were £75.24, £65.00 and £69.00 respectively, and assumed that the unit costs of 3-monthly leuprorelin, goserelin and triptorelin were £225.72, £235.00 and £207.00 respectively. The company also assumed that drug administration was provided in primary care in 50% of cases and in secondary care (by a nurse) in 50% of cases. The company also assumed that treatment initiation costs consisted of a CT and bone scan, a PSA test and a urologist outpatient appointment. It was assumed that patients were followed up by a urologist every 6 months, at which time PSA was measured. The costs of adverse events were calculated based on NHS reference costs, Personal and Social Services Research Unit costs and costs from the published literature. Costs of supportive and palliative care were also included in the model. The company stated that all costs and resource use were validated by UK clinicians.

3.23 The results of the company's base-case analysis showed that degarelix dominated goserelin (that is, it had lower costs and better outcomes compared with goserelin) for treating advanced hormone-dependent prostate cancer. Degarelix provided an additional 0.58 quality-adjusted life years (QALYs) and cost £1697 less than goserelin. The company also presented results for patients with a high risk of disease progression (PSA levels at baseline greater than 20 ng/ml) and for patients with cardiovascular disease at baseline. The results showed that for baseline PSA

levels greater than 20 ng/ml, degarelix dominated goserelin, providing 0.59 additional QALYs and costing £1691 less than goserelin. For patients with cardiovascular disease at baseline, degarelix was associated with increased costs of £6856 and 1.63 additional QALYs compared with goserelin, resulting in an incremental cost-effectiveness ratio (ICER) of £4216 per QALY gained. The company did several sensitivity and scenario analyses varying the assumptions in the model. The results were most sensitive to the assumption that degarelix and LHRH agonists had equivalent efficacy, which resulted in an ICER for degarelix compared with goserelin of £11,274 per QALY gained. The company's probabilistic sensitivity analysis showed that there was a 99.9% probability of degarelix being cost effective compared with goserelin if the maximum acceptable ICER was £20,000 per QALY gained. The company concluded that the key driver of the cost-effectiveness results was the better efficacy and safety profile of degarelix compared with the LHRH agonists.

ERG critique

3.24 The ERG considered that the company's search strategy in the systematic review of clinical effectiveness studies was appropriate and it was satisfied that all relevant randomised controlled trials were identified for the direct comparison of degarelix with LHRH agonists plus short-term anti-androgen treatment. The ERG noted that the company presented data on the clinical efficacy of degarelix based on clinical trials that included patients with all stages of prostate cancer and considered that it would have been preferable to exclude patients with localised or unclassifiable disease from the analyses presented in the company's submission. It further noted that PSA levels for all trials were lower than would be expected in clinical practice and this was likely to be because of the wider inclusion criteria and lower severity of disease in the trial

populations. The ERG obtained advice from clinical experts who highlighted that most patients in the UK who have treatment with LHRH agonists will have anti-androgen flare protection with bicalutamide, and the proportion of patients who had anti-androgen flare protection in the trials was low.

3.25 The ERG noted that the company used several pooled analyses to present the data for adverse events, serum phosphatase levels and PSA progression from the 6 included open-label randomised controlled trials. It considered this 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 was independent, minimising the impact of potential confounding variables. The ERG also noted that the pooled analysis for serum alkaline phosphatase levels should be interpreted with caution, because only the statistically 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. Therefore, the ERG considered that the results presented in pooled analyses in the company's submission (see section 3.12) were inappropriate and should be interpreted with caution.

3.26 The ERG considered the meta-analyses done by the company. It noted that the company did not sufficiently justify the assumption that leuprorelin and goserelin had equivalent efficacy. Furthermore, the results for PSA response showed significant heterogeneity, but the company did not carry out a formal meta-regression in its original submission. The ERG noted that the company included CS35 in some of the meta-analyses, for example when presenting

the results in terms of overall survival, but considered that this trial should have been excluded from these analyses because it used an unlicensed dose of degarelix. Another trial (CS37) had been excluded for similar reasons; it used an intermittent dose schedule of degarelix. The ERG also stated that the use of odds ratios for presenting overall survival results was not appropriate because time points for outcomes such as mortality varied in the included trials and it considered that a hazard ratio best represented these results. Finally, it concluded that the results for overall survival should be interpreted with caution because the studies were of short duration and not designed to detect differences in survival.

3.27 The ERG considered the mixed treatment comparison presented by the company comparing degarelix with the LHRH agonists (goserelin, leuprorelin and triptorelin) and with bicalutamide. The ERG noted the company's conclusion that the non-significant difference in overall survival between the LHRH agonists in the mixed treatment comparison demonstrated equivalence in clinical efficacy and considered that this was not sufficiently justified. The ERG stated that the results of the mixed treatment comparison showed that there was a potential difference in overall survival associated with triptorelin when compared with goserelin and leuprorelin.

3.28 The ERG did a revised mixed treatment comparison that used informative priors for the heterogeneity parameter and the baseline treatment effect, non-informative priors for the treatment effects, and the time points for overall survival from each of the included trials to present the results in terms of hazard ratios. The ERG concluded that the results suggested that there was a small amount of heterogeneity between studies and that triptorelin was associated with lower mortality risk than goserelin and leuprorelin,

and this was statistically significantly lower than leuprorelin (HR 0.28, 95% credible interval 0.07 to 0.95).

3.29 The ERG considered the different assumptions applied in the company's original economic model. It noted the assumption that patients have treatment with degarelix or LHRH agonists until the disease progresses and becomes hormone refractory. The ERG suggested that, in clinical practice, treatment with degarelix or LHRH agonists is not stopped after disease progression and continues until death. The ERG considered that the assumption of equivalent efficacy between all LHRH agonists was not sufficiently justified and that it would have been more appropriate to model the treatment effect of each LHRH agonist individually. The ERG also considered that, although the mixed treatment comparison presented by the company did not include any randomised controlled trials that directly compared degarelix with bicalutamide, an indirect comparison could have been done. The ERG further noted that the benefit of degarelix compared with LHRH agonists in terms of PSA progression had only been shown for 1 year (the duration of CS21), and that the Tombal et al. (2010) study indicated that the difference in PSA recurrence or death was not statistically significant when adjusting for baseline disease stage.

3.30 The ERG heard from its clinical experts that PSA progression should not be used as a universal predictor of mortality and noted that, because of their short duration, the clinical trials were not appropriate for demonstrating a difference in overall survival. Advice from the ERG's clinical experts suggested that it is not clear that there is an overall survival benefit associated with degarelix compared with LHRH agonists. The ERG stated that the company's assumption of a relationship between PSA progression and overall survival based on Hussain et al. (2009) was uncertain and suggested that it was inappropriate to use PSA progression as a

surrogate end point based on the available data from the trials. Therefore, an analysis in which degarelix impacts on PSA progression but not overall survival would have been more appropriate. It also considered that a model structure estimating time to metastatic disease and time to death would have been more appropriate. The ERG stated that it was unable to conduct an exploratory analysis assuming no relationship between PSA progression and overall survival because of the limitations of the company's model structure.

3.31 The ERG noted that the results of the company's pooled analyses of adverse events were included in the economic model. It considered the use of these results to be inappropriate because of the inherent characteristics of pooled analyses (see section 3.25). The ERG also noted the company's assumption that the rate of fractures increased over time for patients having LHRH agonists and decreased over time for patients having degarelix. The ERG suggested that, based on advice from clinical experts, it would have been more appropriate to assume that the rate of fractures would increase over time for both treatment groups and not just for LHRH agonists because suppression of testosterone levels would lead to a reduction in bone mineral density over time.

3.32 The ERG considered that the company's economic model had several limitations. The ERG did additional analyses and presented an updated treatment pathway based on expert opinion. Its scenario analysis assumed that:

- the most appropriate comparator is 3-monthly triptorelin because it is the cheapest LHRH agonist
- treatment with degarelix and LHRH agonists would continue until death, in line with clinical practice and their licensed indications

- a differential treatment effect in PSA progression of degarelix compared with LHRH agonists would only be applied for 1 year, in line with the evidence from CS21
- the proportion of patients having chemotherapy after PSA progression would be 70%, and the proportion of patients having abiraterone would be 70%.

The results of the ERG's scenario analysis based on the above assumptions showed that degarelix provided a gain of 0.247 QALYs compared with triptorelin. This benefit was achieved with an incremental cost of £3659, resulting in an ICER of £14,798 per QALY gained. The ERG did several exploratory analyses and concluded that the cost-effectiveness results were most sensitive to: the exclusion of spinal cord compression adverse events; the modelling of fracture rates; the assumption that PSA progression had an effect on overall survival in patients with metastatic disease; and the assumption of no difference in PSA progression between degarelix and LHRH agonists. The ICER for degarelix when assuming equivalent efficacy between degarelix and LHRH agonists was £35,589 per QALY gained compared with triptorelin (administered every 3 months). This ICER was achieved with an incremental cost of £4166 and a gain of 0.117 QALYs for degarelix compared with triptorelin. The ICERs for degarelix compared with the other LHRH agonists were £28,022 per QALY gained compared with goserelin (administered every 3 months) and £26,186 per QALY gained compared with leuprorelin (administered monthly).

3.33 The ERG did an additional exploratory analysis, correcting for an implementation error in the company's model, and assumed that:

- treatment with degarelix and LHRH agonists would continue until death, in line with clinical practice and their licensed indications

- there is no differential treatment effect of degarelix compared with LHRH agonists in terms of PSA progression or death
- the proportion of patients having chemotherapy after PSA progression would be 70%, and the proportion of patients having abiraterone would be 70%
- the rate of fractures is the same for patients having degarelix and those having LHRH agonists
- the rate of cardiovascular events is the same for patients having degarelix and those having LHRH agonists.

The results from this additional exploratory analysis showed that degarelix provided an incremental cost of £5453 and a QALY gain of 0.053 compared with triptorelin, resulting in an ICER of £103,179 per QALY gained. The ICERs for degarelix when other LHRH agonists were considered ranged from approximately £70,600 per QALY gained (compared with monthly triptorelin) to £105,400 per QALY gained (compared with 6-monthly triptorelin).

3.34 The ERG also did exploratory analyses for patients with spinal metastases with actual or impending spinal cord compression, because expert opinion suggested that this subgroup could potentially benefit more from treatment with degarelix. Because of lack of data to conduct this exploratory analysis, the ERG assumed that patients having degarelix would not have spinal cord compression and that the efficacy of degarelix and LHRH agonists in terms of PSA progression and overall survival was equivalent. The ERG stated that because the rate of spinal cord compression in this subgroup was unknown, it presented the results for rates of 5%, 10% and 50%. The ERG noted that, based on the assumption of equivalent efficacy in terms of PSA progression and overall survival between degarelix and LHRH agonists, the QALY gain for degarelix would be higher compared with triptorelin because of the lower utility decrement associated with spinal cord compression.

The ERG compared the incremental costs associated with treatment and administration for degarelix with those for triptorelin. It concluded that if the rate of spinal cord compression in this subgroup were higher than 3.5%, degarelix would dominate triptorelin (that is, it would be less costly and more effective).

Company's submission of additional evidence

3.35 The company submitted additional evidence in response to consultation. It provided further clarification on PSA progression efficacy data, cardiovascular event data and subgroups for which degarelix offers the greatest benefit. The company also provided new evidence on meta-regression analyses to address the Committee's concerns about pooled analyses from safety and efficacy data in the original submission, an updated clinical pathway treatment algorithm, and additional quality of life and utility values. The company incorporated the results from the meta-regression analyses, the updated treatment pathway and updated utility values into its economic model, and presented updated cost-effectiveness results including 2 new base cases: an updated base case and a conservative base case.

3.36 The company restated degarelix's mechanism of action. It noted that increases in hormone levels (in the form of short-term flare surges, medium- to long-term microsurges and poorer long-term follicle-stimulating hormone control associated with LHRH agonists) may all contribute to faster PSA progression compared with degarelix. The company also noted that the results of the CS21A extension study (see section 3.8) showed that there was a statistically significant decrease in the PSA progression-free survival hazard rate for those patients who switched from having leuprorelin to degarelix, and that this decrease was also observed for follicle-stimulating hormone levels. Therefore, degarelix

provided a differential long-term effect on PSA progression-free survival compared with leuprorelin.

3.37 The company restated that the results published by Albertsen et al. (2013) showed that degarelix provided an additional benefit in reducing the risk of serious cardiovascular adverse events for patients with pre-existing cardiovascular disease. The company stated that LHRH agonists are associated with destabilisation of established vascular lesions and mainly suppress luteinising hormone, whereas degarelix suppresses both luteinising hormone and follicle-stimulating hormone. The receptors for these hormones 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, which may increase the risk of cardiovascular disease.

3.38 The company did non-stratified 1-step, fixed-effects meta-regression to assess trial heterogeneity. All individual patient data were used in 1 regression model to produce a combined result. Meta-regression analyses were done for the following outcomes, with some studies (CS28 and CS31) excluded because they did not contribute events in 1 or both arms of the study:

- PSA progression-free survival (using data from CS21 and CS35).
- Cardiovascular events (using data from CS21, CS35, and CS37).
- Joint-related signs and symptoms (using data from CS21, CS30, CS35 and CS37 for the overall population, and CS21 and CS35 for the baseline PSA greater than 20 ng/ml population).
- Risk of fractures (using data from CS21, CS35, and CS37).

All data from the group of patients who had intermittent doses of degarelix in CS37 were censored (that is, excluded from the analysis from this point onwards) at month 7, so that the analyses only included patients on continuous therapy. The results from the meta-regression analyses for degarelix compared with LHRH agonists were presented as hazard ratios and adjusted for Gleason score, disease stage and baseline PSA.

3.39 For the meta-regression analyses of PSA progression-free survival, data from CS21 and CS35 were used because these were the only trials with the same definition of disease progression (that is, PSA progression or death from any cause, whichever occurred first). The results showed that there was a statistically significant effect on slowing PSA progression in the overall population with degarelix compared with LHRH agonists, but this effect was not statistically significant in patients with PSA levels of more than 20 ng/ml at baseline (the hazard ratio and confidence intervals for PSA progression-free survival were marked as commercial in confidence by the company and therefore cannot be reported here).

3.40 The company did meta-regression analyses for serious cardiovascular adverse events (myocardial infarction, ischaemic cerebrovascular conditions, haemorrhagic cerebrovascular conditions, embolic and thrombotic events, and other ischaemic heart disease). The hazard ratios were adjusted for baseline cardiovascular risk factors, age, BMI and testosterone levels. The results of the meta-regression analyses showed a statistically significant decrease in the risk of serious cardiovascular adverse events for degarelix compared with LHRH agonists, both including and excluding death within 1 year of starting therapy (the hazard ratio and confidence intervals for the risk of serious cardiovascular adverse events were marked as commercial in confidence by the company and therefore cannot be reported here).

3.41 The results of the company's meta-regression analyses for joint-related signs and symptoms showed a statistically significant decrease in risk in the overall population for degarelix compared with LHRH agonists. However, this result was not statistically significant for patients with PSA levels of more than 20 ng/ml at baseline (the hazard ratio and confidence intervals for joint-related signs and symptoms were marked as commercial in confidence by the company and therefore cannot be reported here).

3.42 The results of the company's meta-regression analyses for fractures did not show statistically significant differences between degarelix and LHRH agonists for patients with PSA levels of more than 20 ng/ml at baseline. The company noted that in its original submission, it had assumed proportional hazards between the 2 treatment groups. It stated that this is unlikely to be accurate, because prostate cancer disease-related events such as pathological fractures are more likely to occur early on and osteoporotic fractures become more common with increasing age. Degarelix is likely only to reduce the rate of pathological fractures. Therefore, the company incorporated a scenario analysis in which the risk of fractures was increased for patients having degarelix to give an equal risk of fractures between degarelix and LHRH agonists from year 2 onwards. The company noted that patients having either degarelix or LHRH agonists have an increased risk of fractures over time, and so the curves for fracture rate are likely to either stop separating or converge.

3.43 The company presented updated utility values based on the Committee's preferred mapping algorithm by McKenzie and van der Pol (2009). The company also noted the Committee's concerns about the possibility of double counting the effect of adverse events on health-related quality of life. It amended the utility values for patients not having an adverse event by PSA progression status to

ensure there was no double counting for adverse events in the model.

3.44 The company presented an updated economic model that included the following changes:

- inclusion of the results from the 1-step fixed-effects meta-regression model for safety and efficacy data
- additional scenario analyses for the data used to fit the curves for PSA progression for degarelix
- an updated treatment pathway in which enzalutamide was included after docetaxel and abiraterone, and abiraterone was also considered for use before docetaxel
- change in the comparator drug cost to a weighted average of 3-monthly LHRH agonists used in the UK, based on sales figures
- continuation of first-line hormonal therapy until death
- updated utility values derived from the mapping algorithm published by McKenzie and van der Pol (2009).

3.45 The results of the company's updated base-case analysis for degarelix compared with LHRH agonists estimated incremental costs of £904 and incremental QALYs of 0.331, resulting in an ICER of £2733 per QALY gained. For patients with PSA levels of more than 20 ng/ml at baseline, the estimated incremental costs and QALYs were £1396 and 0.310 respectively, leading to an ICER of £4509 per QALY gained. The company also included a subgroup analysis for patients with locally advanced or metastatic prostate cancer. This analysis estimated incremental costs and QALYs of £1696 and 0.259 respectively, resulting in an ICER of £6539 per QALY gained.

3.46 The company also presented its conservative base-case analysis, based on the changes included in the updated base case (see section 3.45) together with the assumptions of equal efficacy for degarelix and LHRH agonists after 1 year, and no benefit in reducing the risk of fractures for degarelix compared with LHRH agonists (implemented in the economic model by excluding fracture rates in both treatment groups). For degarelix compared with LHRH agonists, the model estimated incremental costs and QALYs of £3460 and 0.177 respectively, resulting in an ICER of £19,510 per QALY gained for the overall population. For patients with a PSA level of more than 20 ng/ml at baseline, the model estimated incremental costs and QALYs of £3311 and 0.189 respectively, resulting in an ICER of £17,516 per QALY gained. For patients with locally advanced or metastatic disease, the model estimated incremental costs and QALYs of £3460 and 0.166 respectively, resulting in an ICER of £20,847 per QALY gained.

ERG's critique of the company's submission of additional evidence

3.47 The ERG reviewed and critiqued the company's submission of additional evidence. Overall, the ERG considered that the company's additional evidence was not based on robust analyses and suggested that the ERG's results presented in the original appraisal consultation document (see section 3.33) were most appropriate to inform decision-making.

3.48 The ERG considered that there was a need for direct evidence to confirm the potential underlying mechanism of action of degarelix and the causal conclusions of the company's findings for PSA progression with degarelix compared with LHRH agonists (see section 3.36). It also noted that CS21A did not include a comparator group and so it was not possible to support the

company's claim of a statistically significant difference in PSA progression-free survival for degarelix compared with LHRH agonists.

3.49 The ERG discussed the company's meta-regression analyses for PSA progression-free survival, cardiovascular events, joint-related signs and symptoms, and risk of fractures. It noted that the company used non-stratified 1-step, fixed-effects meta-regression models. The ERG considered that a stratified model would have been more appropriate to preserve randomisation within studies. Furthermore, random-effects models produce more uncertainty, allow for residual heterogeneity among treatment effects not modelled by the explanatory variables, and lead to less favourable results than fixed-effects models. The ERG restated that including CS35 in the analyses was inappropriate because it included an unlicensed dose of degarelix (see section 3.26). It noted that although the company stated there was no heterogeneity between the trials in the meta-regression analyses for all outcomes, this had not been appropriately assessed. The ERG noted that the interaction between trial and treatment had been adjusted together with several baseline covariates in the company'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. The ERG also stated that it was unclear whether the 2 groups of patients in CS21 (having the licensed and unlicensed doses) were included in the meta-regression analyses. The ERG concluded that the company's meta-regression analyses were subject to several limitations.

3.50 The ERG considered the results of the company's meta-regression analyses for PSA progression-free survival in which data from

CS21 and CS35 were combined. It noted that it was unclear whether the definition of PSA progression-free survival was the same in CS21 and CS35, and so considered it inappropriate to combine both trials in the analyses. The ERG noted that, although the adjusted hazard ratio from the meta-regression analyses for PSA progression-free survival was statistically significant for degarelix compared with LHRH agonists in the overall population, it was not significant for patients with PSA of more than 20 ng/ml at baseline and for patients with locally advanced or metastatic disease (the hazard ratio and confidence intervals for PSA progression-free survival were marked as commercial in confidence by the company and therefore cannot be reported here). Moreover, the ERG stated that the claim that the benefit of degarelix will be roughly equivalent or greater in patients with PSA of more than 20 ng/ml at baseline than the observed hazard ratio is misleading because the company had already adjusted for baseline risk. The ERG concluded that the company's meta-regression results for PSA progression-free survival were associated with several limitations.

3.51 The ERG noted that the results of the meta-regression analyses for the risk of cardiovascular events resulted in a hazard ratio that was more plausible in terms of statistical significance than the results of the company's original pooled analyses. However, it noted that when compared with the results of the individual trials, the results of the meta-regression analysis were implausible because they had more favourable p values than the individual trials. The ERG noted that this was likely to be a result of using the fixed-effects model, which assumes that the treatment effect was the same and leads to a more favourable pooled estimate than it should be.

3.52 The ERG reviewed the changes to the company's model and the updated cost-effectiveness results. It stated that it was appropriate

to use the updated utility values obtained with the mapping algorithm from McKenzie and van der Pol (2009) and the assumption that hormonal therapy would be continued until death in line with clinical practice. The provision of additional scenario analyses was also appropriate. However, the ERG expressed concern about the use of the meta-regression results in the model because of the limitations associated with these analyses. It also noted that using a weighted average cost for the comparator drug costs was not appropriate, and that including enzalutamide in the treatment pathway in sequence after abiraterone was not consistent with the recently issued draft guidance for the appraisal of enzalutamide for treating hormone-relapsed metastatic prostate cancer. The ERG also noted that there were some implementation errors in the company's original model that persisted in the updated model. It observed that the conservative base case, in which the company assumed fracture risk to be equal with both degarelix and LHRH agonists, actually excluded fractures from the model for both treatment groups. The ERG also highlighted that the company did not present a subgroup analysis for patients with pre-existing cardiovascular disease. Overall the ERG considered that the company's meta-regression and updated cost-effectiveness analyses were not appropriate to inform decision-making, and stated that the results presented in the appraisal consultation document based on the original model (see section 3.33) were the most appropriate for consideration.

Additional work commissioned from the Decision Support Unit (DSU)

3.53 In line with the Guide to the processes of technology appraisal, the NICE Decision Support Unit (DSU) was commissioned to undertake further work on the subgroup of people with metastatic hormone-dependent prostate cancer who have spinal metastases.

It specifically explored the estimates of the rate of spinal cord compression in people with metastatic hormone-dependent prostate cancer with spinal metastases from the prostate and, if sufficient data were available, the cost effectiveness of degarelix compared with the LHRH agonists in people with spinal metastases from the prostate.

3.54 The DSU did a rapid and focused systematic review to identify any relevant evidence on the rates of spinal cord compression in people with metastatic hormone-dependent prostate cancer who had treatment with LHRH agonists or degarelix. It identified 2 relevant studies: a study by Oh et al. (2010) that was also used by the company and the ERG in the original model, and a study by Ahmann et al. (1987). The DSU noted limitations in the study by Ahmann et al; it was done in the 1980s, included a small number of people, and people in the study did not have anti-androgen therapy to reduce the risk of testosterone flare. The DSU concluded that the study by Oh et al. represented the best available evidence. The study reported that, in people with metastatic hormone-dependent prostate cancer, the rate of spinal cord compression within 30 days of having LHRH agonists was 0.96%. The DSU did not find any evidence in the subgroup of patients with spinal metastases from the prostate, and did not find any evidence relating to the incidence of spinal cord compression in people who had treatment with degarelix.

3.55 The DSU identified an autopsy study by Bubendorf et al. (2000) which reported that of 631 people with metastatic prostate cancer, 501 had bone metastases. Of these patients, 447 had spinal metastases. This study was used to estimate the proportion of people with metastatic disease who had spinal metastases (approximately 71%) and the DSU noted that this estimate would represent an upper limit. It also stated that this study had several

limitations including that patients in the study would likely have had hormone-resistant, rather than hormone-dependent metastatic prostate cancer and thus, any analysis based on this estimate should be considered with caution.

3.56 For the economic analysis, the DSU used the company's model comparing degarelix with LHRH agonists that was amended by the ERG (see section 3.33). The DSU noted that the rate of spinal cord compression in people with spinal metastases would be approximately 1.35% when assuming that:

- the upper limit on the proportion of people with metastatic prostate cancer who have spinal metastases was 71%
- the rate of spinal cord compression in people with metastatic hormone-dependent prostate cancer was 0.96%
- spinal cord compression is only possible in people with spinal metastases.

3.57 The DSU did sensitivity analyses, varying the rate of spinal cord compression in the model for people with locally advanced or metastatic hormone-dependent prostate cancer. It noted that the ICERs for degarelix compared with LHRH agonists were:

- for an assumed rate of spinal cord compression of 1%: £99,228, £82,792 and £78,832 per QALY gained compared, respectively, with triptorelin (3-monthly), goserelin (3-monthly) and leuprorelin (monthly)
- for an assumed rate of spinal cord compression of 2%: £39,163, £28,920 and £26,452 per QALY gained compared, respectively, with triptorelin (3-monthly), goserelin (3-monthly) and leuprorelin (monthly)
- for an assumed rate of spinal cord compression of 3%: £11,974, £4534 and £2742 per QALY gained compared, respectively, with

triptorelin (3-monthly), goserelin (3-monthly) and leuprorelin (monthly)

- for an assumed rate of spinal cord compression of 4%, degarelix dominated (that is, it had lower costs and better outcomes) triptorelin (3-monthly). Degarelix dominated leuprorelin (monthly) and goserelin (3-monthly) at an assumed spinal cord compression rate of 3.5%.

3.58 The DSU also did sensitivity analyses using the model for the whole population with locally advanced or metastatic hormone-dependent prostate cancer, incorporating the estimated rates of spinal cord compression from the subgroup of people with metastatic prostate cancer and the subgroup of people with spinal metastases. It noted that this approach is subject to important limitations and uncertainty because it uses the model parameters and assumptions for the whole population. Because of a lack of any other evidence, the DSU used these assumptions as a representation of the subgroup analyses for people with metastatic prostate cancer and for those with spinal metastases. The results showed that the ICERs for degarelix compared with LHRH agonists were:

- for an assumed rate of spinal cord compression of 0.96% (reflective of the estimated rate of spinal cord compression in people with metastatic prostate cancer): £103,179, £86,335 and £82,277 per QALY gained compared, respectively, with triptorelin (3-monthly), goserelin (3-monthly) and leuprorelin (monthly)
- for an assumed rate of spinal cord compression of 1.35% (reflective of the estimated rate of spinal cord compression in people with spinal metastases): £71,387, £57,821 and £54,552 per QALY gained compared, respectively, with triptorelin (3-monthly), goserelin (3-monthly) and leuprorelin (monthly).

The DSU stated that because of lack of data on the population size and of the spinal cord compression rate for the spinal metastases subgroup, it was not possible to accurately estimate the cost-effectiveness of degarelix for this subgroup.

3.59 Full details of all the evidence are in the Committee papers.

4 Consideration of the evidence

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 experts. It also took into account the effective use of NHS resources.

4.1 The Committee discussed the current management of advanced hormone-dependent prostate cancer. It heard from the clinical experts that luteinising hormone-releasing hormone (LHRH) agonists (leuprorelin, goserelin and triptorelin) are first-line treatments for hormone-dependent prostate cancer, and that clinicians consider each LHRH agonist to have equivalent clinical efficacy. The clinical experts also stated that, in clinical practice, treatment with LHRH agonists continues after the disease has progressed and until death. The clinical experts 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. The Committee noted the updated treatment pathway presented by the company in the submission of additional evidence; this positioned abiraterone before docetaxel, and enzalutamide before chemotherapy and

abiraterone. The Committee understood that although there may be variation in clinical practice, the updated treatment pathway presented by the company is not consistent with current NICE guidance (NICE technology appraisal guidance on abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen and enzalutamide for treating metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen). The Committee heard from the clinical experts that the appropriate place for degarelix in the treatment pathway is as an alternative to LHRH agonists. The Committee noted comments received during consultation that indicated the usefulness of having guidance for ongoing treatment with hormonal therapy once testosterone levels have been suppressed to castration levels with degarelix, and the possibility of switching to LHRH agonists afterwards in the interests of cost savings. The Committee noted that it can only make recommendations on the technology under appraisal and within the boundaries of its marketing authorisation. The Committee considered that the likely position of degarelix in the treatment pathway is as first-line hormonal therapy for treating advanced hormone-dependent prostate cancer; that is, at the same point in the pathway as the LHRH agonists.

4.2 The Committee heard from the clinical experts that degarelix is particularly appropriate for people at high risk of disease progression (who have a prostate-specific antigen [PSA] level of more than 20 ng/ml), older people, those with pre-existing cardiovascular disease, and people with spinal metastases from the prostate (some of whom may go on to develop spinal cord compression). The Committee acknowledged that the NICE guideline on metastatic spinal cord compression states that symptoms suggestive of metastatic spinal cord compression may

include: progressive pain in the spine, severe unremitting spinal pain, spinal pain aggravated by straining, pain described as 'band like', localised spinal tenderness, nocturnal spinal pain preventing sleep, neurological symptoms such as radicular pain, limb weakness, difficulty in walking, sensory loss, and bladder or bowel dysfunction. It also states that if a patient with a diagnosis of cancer has neurological symptoms or signs suggestive of metastatic spinal cord compression, a magnetic resonance imaging (MRI) scan should be arranged within 24 hours and occasionally sooner if there is a pressing clinical need for emergency surgery. The Committee concluded that consideration should be given to the subgroups highlighted by the clinical experts; that is, people at high risk of disease progression (who have a prostate-specific antigen [PSA] level of more than 20 ng/ml), older people, those with pre-existing cardiovascular disease, and people with spinal metastases from the prostate (some of whom may go on to develop spinal cord compression).

4.3 The Committee heard from the patient experts that people want to avoid the adverse events and discomfort associated with the later stages of prostate cancer. Patient experts stated that advanced prostate cancer is a diverse disease and people respond differently to treatments, so the availability of a range of treatment options is important. The Committee heard from the patient experts that degarelix appears to offer long-term clinical benefit, which is particularly important for people with advanced disease. They also noted that the safety profile of degarelix is comparable to that of the LHRH agonists and the potential benefits of degarelix outweigh the adverse effects associated with it. Patient experts noted that subcutaneous injections of degarelix are administered monthly and this dosing schedule may be inconvenient for some patients compared with the administration of LHRH agonists which is every

3 months. The Committee concluded that degarelix may offer an additional option for people with advanced hormone-dependent prostate cancer.

4.4 The Committee discussed the decision problem presented in the company's submission. It noted that the appraisal scope listed bicalutamide monotherapy as a comparator, but this comparison was not included in the company's submission. The Committee noted that the company did not identify any head-to-head trial evidence comparing degarelix with bicalutamide monotherapy. It noted the Evidence Review Group (ERG)'s comment that it may have been possible to conduct a naive indirect comparison. The Committee heard from the clinical experts that in clinical practice, treatment with bicalutamide monotherapy is limited to a very small group of people, particularly those for whom preservation of sexual function is important and those who are willing to accept the adverse effects of the treatment, such as reduced overall survival and liver problems. The Committee concluded that, based on the available evidence and UK clinical practice, it supported the company's view that comparing degarelix with bicalutamide monotherapy was not appropriate.

Clinical effectiveness

4.5 The Committee considered the main clinical effectiveness evidence for degarelix compared with leuprorelin from the CS21 randomised controlled trial and the CS21A extension study. It also considered the evidence presented by the company from randomised controlled trials of degarelix compared with other LHRH agonists (CS28, CS30, CS31, CS35 and CS37). It heard from the clinical experts and the ERG that in clinical practice, people having hormonal therapy with LHRH agonists also have 28 days treatment with bicalutamide for protection against testosterone flare. The

Committee noted that in CS21 only 11% of patients in the leuprorelin group had flare protection with bicalutamide and it considered this to be inconsistent with UK clinical practice. The Committee also noted that the 6 trials of degarelix compared with LHRH agonists included patients with all stages of prostate cancer, and that a large proportion of these had non-classifiable prostate cancer (approximately 19% of the patients in CS21). The Committee also noted that some of the trials included in the company's submission used unlicensed doses and regimens of degarelix, which may have had an impact on the results of these studies. The Committee concluded that the generalisability of the trials' results to UK clinical practice was limited.

4.6 The Committee discussed the clinical-effectiveness results presented in the company's submission. It noted that all 6 studies were open label and primarily designed as non-inferiority trials and that the primary end point in the main clinical trial (CS21) was suppression of testosterone levels. It noted that in CS21 the licensed dose of degarelix (240/80 mg) resulted in a rapid suppression of testosterone to castration levels compared with leuprorelin, and that fewer patients had testosterone flare with degarelix than with LHRH agonists. It also noted that a non-inferior probability of achieving testosterone levels of 0.5 ng/ml or less from days 28 to 364 was observed for degarelix compared with LHRH agonists (see section 3.3). 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. This is particularly important in people with spinal metastases from the prostate, some of whom may develop spinal cord compression, because there may be a relationship between the testosterone flare when hormonal treatment starts and spinal cord compression.

4.7 The Committee considered the results from CS21 for the PSA progression end point. It noted that there was a statistically significant difference between degarelix and leuprorelin for the median percentage change in PSA levels (see section 3.4). The Committee also noted that post-hoc analyses of subgroups from CS21 showed that there was no statistically significant difference between treatment groups in the proportion of patients with metastatic disease who experienced PSA progression, and this was also similar in patients with locally advanced disease (see section 3.5). The Committee noted the post-hoc analyses of CS21 published by Tombal et al. (2010) that showed 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 (see section 3.6). The Committee heard from the clinical experts that it was not possible to say whether a difference in PSA progression is observed for degarelix compared with LHRH agonists in clinical practice. The Committee noted the company's statement in the submission of additional evidence that the results of the CS21A extension trial supported the statistically significant difference in PSA progression-free survival between degarelix and leuprorelin (see section 3.36). It also noted the ERG's comment that this difference between degarelix and leuprorelin was not in fact demonstrated in CS21A, because it was a single arm trial (that is, it did not include a comparator group) and all patients who had leuprorelin in CS21 switched from leuprorelin to degarelix (see section 3.48). The Committee noted the results of the company's pooled analyses from the company's original submission, together with the results of the meta-regression analyses for PSA progression-free survival (using data from CS21 and CS35) which were presented in the company's submission of additional evidence (see section 3.39). It was aware of the ERG's comments that

pooled analyses should be interpreted with caution and that the company's meta-regression analyses had substantial limitations (see section 3.50). The Committee discussed the differences between a random-effects model and a fixed-effects model for the meta-regression analyses. It understood that, although the point estimate overall would be expected to be similar in both models, the random-effects model assumes that each trial may estimate different treatment effects. The observed variation is therefore 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 estimate the same treatment effect and any observed variation is simply the result of sampling error. The Committee 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 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 also noted that the results from the meta-regression analyses showed that the difference between degarelix and LHRH agonists in PSA progression-free survival for people with PSA levels of more than 20 ng/ml at baseline and for people with locally advanced or metastatic prostate cancer was not statistically significant. In addition, it noted that the ERG stated that the company's claim that the benefit of degarelix will be roughly equivalent or greater in

people with PSA levels of more than 20 ng/ml at baseline than the observed hazard ratio is misleading because the manufacturer had already adjusted for baseline PSA level. The Committee considered that the results for PSA progression and long-term PSA progression benefit for degarelix compared with LHRH agonists were highly uncertain. It concluded that no PSA progression benefit from degarelix compared with LHRH agonists could be assumed and therefore this proposed subgroup of people at high risk of disease progression (that is, people with PSA levels of more than 20 ng/ml at baseline) was not considered further.

4.8 The Committee discussed the results of the company's mixed treatment comparison for overall survival, and the ERG's comments and revised mixed treatment comparison. The Committee noted that the duration of the trials was short and they were not sufficiently powered to detect differences in overall survival between treatments. It further noted that the absolute number of deaths in the trials was small (see sections 3.7 and 3.13). The Committee also noted that the results of the company's mixed treatment comparison did not show statistically significant differences in overall survival for degarelix compared with each of the LHRH agonists and between the different LHRH agonists themselves. It noted the company's conclusion that the results showed equivalent clinical efficacy between LHRH agonists. The Committee heard from the clinical experts that in clinical practice, all the LHRH agonists are regarded as having equivalent clinical efficacy, and no additional overall survival benefit has been observed with triptorelin compared with leuprorelin or goserelin. The Committee concluded that it was plausible to assume equivalent clinical efficacy between LHRH agonists, but there was a lack of robust evidence to support an overall survival benefit with degarelix compared with LHRH agonists.

4.9 The Committee discussed the results of the company's pooled post hoc analyses of adverse events from the 6 degarelix trials, and the meta-regression analyses for fractures that were presented in the company's submission of additional evidence. The Committee noted the ERG's concerns about the robustness of the pooled analyses and the limitations of the company's meta-regression analyses (see section 3.49). The Committee noted that the company acknowledged that the rate of fractures is likely to increase in people having either degarelix or LHRH agonists, and that the results from the meta-regression analyses showed no statistically significant difference between degarelix and LHRH agonists in reducing the risk of fractures. The Committee also considered the scenario analysis presented by the company in which the fracture risk was modelled with increased hazards for degarelix to give an equal risk of fractures to LHRH agonists at 2 years. The Committee heard from the clinical experts and the ERG that the risk of fractures would be expected to increase in both groups over time as a result of a decrease in bone mineral density. The Committee heard from the clinical experts that the duration of the trials was not long enough to demonstrate changes in bone mineral density and so these results should be considered exploratory. The Committee concluded that there was a high degree of uncertainty about any difference in the rate of fractures for degarelix compared with LHRH agonists, and therefore no difference between fracture rates could be assumed between treatment groups.

4.10 The Committee considered the results of the company's pooled analysis from its original submission and the meta-regression analyses for cardiovascular events that were presented in the company's submission of additional evidence. 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 company's original pooled analyses, but when compared with the results of the individual trials the result was implausible (see section 3.51). The Committee also noted that the results of a study by Albertsen et al. (2013) showed a statistically significant reduction in the risk of a cardiovascular event with degarelix compared with LHRH agonists in people with pre-existing cardiovascular disease (see section 3.12). The Committee noted comments received during consultation and the views of the clinical experts which suggested that degarelix may be particularly beneficial for people with pre-existing cardiovascular disease; treatment with LHRH agonists is associated with an increased risk of cardiovascular events because of changes in blood lipids, increased plasma insulin levels and increased risk of metabolic syndrome. The Committee understood that the increase in conventional cardiovascular risk factors was due to androgen deprivation and was aware that degarelix, used within its marketing authorisation, was non-inferior to leuprorelin in producing androgen deprivation by suppressing testosterone to castration levels. The Committee noted that the definition of cardiovascular disease in the company'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 end points. Furthermore, the patients included in the company's analysis were a subgroup of a subgroup and this reduced the power and robustness of the analysis and conclusions. The Committee was aware of Albertsen et al.'s conclusion that, because their study had 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 heard from the company that there are several hypotheses for the possible benefit of degarelix compared with LHRH agonists in reducing the risk of cardiovascular events in people with pre-existing cardiovascular disease, including suppression of both luteinising hormone and follicle-stimulating hormone and degarelix's potential effect of reducing inflammation linked with atherosclerosis. The Committee noted comments received during consultation outlining the potential benefits of degarelix compared with LHRH agonists in people with pre-existing cardiovascular disease, and discussed in detail the clinical evidence presented for this subgroup. It concluded that, because of the uncertainty around both the pooled analyses and the meta-regression analyses presented by the company, 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.

4.11 The Committee heard from the clinical experts that there may be a relationship between the testosterone flare when hormonal treatment starts and spinal cord compression in people with spinal metastases from the prostate. The risk of spinal cord compression may be lower in people having degarelix compared with LHRH agonists because degarelix does not produce an initial flare in testosterone levels. The clinical experts acknowledged that degarelix is not a treatment for spinal cord compression but agreed that it may provide an additional clinical benefit for the subgroup of people with spinal metastases from the prostate who may develop spinal cord compression. The Committee explored the wording in

the NICE guideline on metastatic spinal cord compression. It asked for the views of the experts and the company on whether the signs and symptoms suggestive of spinal cord compression, as specified in the guideline, would help to accurately define a subgroup of people who may develop spinal cord compression. The Committee heard from the patient experts that some of the symptoms specified in the guideline are not only associated with metastatic spinal cord compression but are quite common in people with prostate cancer. The Committee also heard from some of the patient and clinical experts that it would not be appropriate to wait until people present with signs and symptoms that could be suggestive of spinal cord compression to start degarelix, because it is not a treatment for spinal cord compression and any benefit would be limited at this stage in the disease process which would be too late for preventing the event to occur. The Committee recalled comments received during consultation and clinical advice to the ERG that degarelix could be useful for people with actual or impending spinal cord compression from the prostate (that is, people who present with signs and symptoms of spinal cord compression) because it could not exacerbate spinal cord compression, since it does not produce a testosterone flare. The clinical experts noted that, to reduce the risk of a testosterone flare, patients would usually have concomitant treatment with bicalutamide for at least 7 days before starting LHRH agonist therapy whereas testosterone suppression with degarelix would be expected to be immediate. The difference in clinical benefit from these 2 approaches was unknown. The Committee also heard from the clinical experts that in clinical practice there can be delays in the access to an immediate MRI scan and that many people would not be seen by a specialist at disease presentation as stated in the guideline (see section 4.2), so these people cannot be easily and quickly identified. The clinical experts also noted that it would not be appropriate to do an MRI

scan for all patients with spinal metastases from the prostate. The clinical experts acknowledged the difficulty in identifying bone metastases that may lead to spinal cord compression, and that this is exacerbated when attempting to identify metastases from the prostate that would lead to spinal cord compression solely as a result of a testosterone flare associated with LHRH agonists. The Committee heard from the clinical experts that spinal cord compression can occur as a result of a single metastasis in the spine and also in people with more extensive disease. The patient and clinical experts also noted that they were not aware of any other tests or methods that would distinguish a subgroup of people with spinal metastases from the prostate who may develop spinal cord compression. The experts acknowledged that there is no evidence to support the use of degarelix in this subgroup beyond their experience in clinical practice. They noted that spinal cord compression caused by metastases from the prostate was an uncommon event and therefore it is difficult to estimate its incidence across clinical practice in England. The patient experts noted that a clear definition of the patient population is needed, with a simple definition being preferred. The Committee understood from the company and from the clinical and patient experts that degarelix would be considered suitable for all people with prostate cancer and spinal metastases, because they may develop spinal cord compression. The Committee concluded that, although degarelix could offer particular benefit for people with spinal metastases who may develop spinal cord compression (because, unlike LHRH agonists, it does not produce an initial surge in testosterone levels, which is potentially associated with spinal cord compression), it is difficult to identify which people with spinal metastases would develop spinal cord compression directly as a result of the testosterone surge that can occur with LHRH agonists. The Committee concluded that it is not possible to reliably identify

and precisely define a subgroup of patients who face a higher risk of developing spinal cord compression from the broader population of patients with spinal metastases from the prostate.

4.12 The Committee noted the NICE Decision Support Unit (DSU)'s work on the subgroup of people with metastatic hormone-dependent prostate cancer with spinal metastases from the prostate (see sections 3.53 – 3.56). It noted that this specifically explored the estimate of the rate of spinal cord compression in this subgroup with metastatic hormone-dependent prostate cancer with spinal metastases from the prostate. The Committee noted that the DSU did not find any new evidence that would help the Committee to better identify and clearly define the subgroup of people with spinal metastases from the prostate who may develop spinal cord compression as a result of testosterone flare associated with LHRH agonists and who might benefit most from degarelix. It specifically noted that the DSU did not find any evidence in the subgroup of patients with spinal metastases from the prostate and that based on an autopsy study that was subject to substantial limitations it derived with high uncertainty the estimated rate of spinal cord compression in this subgroup (see section 3.54). The Committee was aware of the DSU statement that because of the high degree of uncertainty on the rate of spinal cord compression in people with spinal metastases any analysis based on this estimate should be considered with caution. Therefore the Committee considered that this estimate was not robust enough to use for decision-making in this subgroup. The Committee also noted that the DSU confirmed that the best evidence available for the rate of spinal cord compression in people with locally advanced or metastatic hormone-dependent prostate cancer remained the study by Oh et al. (2010) and it heard from the clinical experts that they were not aware of any other evidence apart from this study. The Committee

concluded that the work presented by the DSU provided further confirmation of the fact that it is not possible to clearly identify and define a subgroup of people who may develop spinal cord compression as a result of a testosterone flare from those people with spinal metastases from the prostate, and that the best evidence available for estimating the rate of spinal cord compression in people with metastatic hormone-dependent prostate cancer was the study by Oh et al.

Cost effectiveness

4.13 The Committee discussed the cost-effectiveness evidence presented in both the company's original submission and the submission of additional evidence (which was received in response to consultation) for people with advanced hormone-dependent prostate cancer (see section 3.35). The Committee noted that clinical-effectiveness data for the model were derived from CS21, CS21A and CS35, and that the data for adverse events were derived from the meta-regression analyses (see section 3.38). The Committee was aware of its previous discussion about the equivalent clinical efficacy between LHRH agonists (see section 4.8) and concluded that it was plausible to assume equivalent clinical efficacy between LHRH agonists in the model.

4.14 The Committee discussed the clinical-effectiveness data for PSA progression used in the company's model. It was aware that PSA progression was the main driver of disease progression in the model, but it had concluded that a PSA progression benefit for degarelix compared with LHRH agonists was highly uncertain (see section 4.7). The Committee concluded that the company's assumption of differential PSA progression for degarelix compared with LHRH agonists was not proven.

4.15 The Committee considered the company's assumption of a link between PSA progression on first-line treatment and an increased risk of mortality for people with metastatic disease in the economic model. Assuming that there was a link, delayed progression from the first-line treatment states would result in a lower mortality risk, and therefore an overall survival benefit for degarelix compared with goserelin. It noted that in CS21 there was no statistically significant difference between degarelix and leuprorelin for PSA progression or death after adjusting for baseline PSA level and disease stage. It also noted the ERG's concern that, because of the short duration of CS21 and because it was not powered to detect differences in survival, it was not appropriate to extrapolate the relationship between PSA progression and overall survival over a long time horizon based on the trial data. The clinical experts stated that, although PSA progression is a good indicator of treatment response, caution should be taken when using it as a surrogate outcome for extrapolating long-term overall survival. The Committee acknowledged that there was no robust evidence to support any overall survival benefit for degarelix compared with LHRH agonists (see section 4.8) and concluded that no overall survival benefit for degarelix compared with LHRH agonists should have been assumed in the model.

4.16 The Committee noted that the results of the company's meta-regression analyses for fractures, joint-related signs and symptoms, and cardiovascular events were used in the economic model. It was aware that these analyses lacked robustness and that there was a high degree of uncertainty around the results (see sections 4.9 and 4.10). It noted that the results of the company's meta-regression analyses showed no statistically significant difference between degarelix and LHRH agonists in reducing the risk of fractures. It also noted that the results of the company's

meta-regression analyses for cardiovascular events were implausible when compared with the results of the individual trials (see section 4.10), and that the results of the study by Albertsen et al. (2013) should be interpreted with caution due to the limitations of the study. The Committee further noted that when extrapolating the results over a long time horizon, the assumed benefit of degarelix was even greater. The Committee concluded that there was considerable uncertainty around the estimated differences in the rates of fractures and cardiovascular events for degarelix compared with LHRH agonists. Therefore, it would have been more appropriate to assume no differences for the rate of cardiovascular events and fractures between degarelix and LHRH agonists in the model.

4.17 The Committee discussed the updated utility values that were applied in the company's model and included in the submission of additional evidence in response to consultation. It noted that the company's updated model used the mapping algorithm from McKenzie and van der Pol (2009), which the Committee had agreed was the most appropriate method to transform health-related quality-of-life data into utility values at its first meeting. This was because it included around 20 times as many observations as the Kontodimopoulos et al. (2009) algorithm used in the company's original model, it had been validated by external data sources (thereby improving its generalisability), and it used all the EORTC QLQ-C30 domain scores in the equation to predict EQ-5D utility scores. The Committee noted that the impact of using the McKenzie and van der Pol algorithm on the incremental cost-effectiveness ratio (ICER) for degarelix compared with LHRH agonists was small. The Committee concluded that using the utility algorithm by McKenzie and van der Pol was an appropriate change to the model.

4.18 The Committee considered the changes in the updated economic model (see section 3.44) and agreed with the ERG's assumption of hormonal therapy continuing until death in line with clinical practice. The Committee also agreed with the ERG that it was not appropriate to use the results from the meta-regression analyses because of their limitations (see section 3.49) and the changes in the treatment pathway, because including the use of enzalutamide and abiraterone before docetaxel is not consistent with current NICE guidance (see section 3.52).

4.19 The Committee discussed the company's updated cost-effectiveness results from the economic model for people with advanced hormone-dependent prostate cancer. It noted that in the company's submission of additional evidence in response to consultation, the company had presented a probabilistic estimate of the ICER, 2 base-case scenarios (an updated base case and the company's conservative base case) and cost-effectiveness estimates for different subgroups (see sections 3.45 and 3.46). The Committee noted that in the company's updated base-case analysis for degarelix compared with LHRH agonists, the ICER was £2730 per quality-adjusted life year (QALY) gained. It noted that these results were still based on assumptions of greater clinical efficacy in terms of PSA progression, overall survival, reducing fracture rates over the first 2 years, and reducing cardiovascular events with degarelix compared with LHRH agonists. It noted its earlier conclusions that the evidence informing these assumptions was subject to a high degree of uncertainty. The Committee also noted the ERG's comments that in the company's conservative base-case analysis, the company excluded the risk of fractures in both groups in the model (instead of assuming the same rate in both groups), and the Committee considered this to be inappropriate. Therefore, the Committee concluded that the

company's conservative base case was not appropriate for decision-making. It further concluded that the company's updated base-case ICER was still based on implausible assumptions that were likely to underestimate the true incremental cost per QALY gained of degarelix compared with LHRH agonists.

4.20 The Committee considered the ERG's assumptions used in its original exploratory analyses (see section 3.32). It noted that the ERG used triptorelin as the comparator in its base-case analysis, based on the results of its mixed treatment comparison and because it was the least costly LHRH agonist. The Committee was aware of the comments from the clinical experts that all LHRH agonists were regarded as having equivalent clinical efficacy. The Committee agreed with the ERG that it was plausible to assume that treatment with degarelix and LHRH agonists would continue until death based on the clinical experts' opinion on current UK clinical practice. The Committee considered the ERG's assumption of no difference in PSA progression between degarelix and LHRH agonists and was aware of its earlier conclusion that the evidence to support any overall survival benefit for degarelix compared with LHRH agonists was highly uncertain (see section 4.15). It therefore concluded that no differences in PSA progression or death should be assumed in the model. The Committee considered, based on the clinical experts' statements and the ERG's comments, that the proportion of people having chemotherapy in clinical practice would be lower than the 70% assumed in the ERG's exploratory analyses, and it understood that this proportion would represent an upper limit. The ERG mentioned that changes to these proportions did not have a large impact on the ICER. The Committee noted the ERG's comments that the assumptions applied in its additional exploratory analysis, which used the Committee's preferred assumptions agreed at the first meeting (see section 3.33) and which were used

to formulate the Committee's preliminary recommendations, were the most appropriate to inform decision-making. The Committee noted that, in the ERG's additional exploratory analyses, the ICER for degarelix compared with 3-monthly triptorelin was £103,200 per QALY gained (using its preferred assumptions of no differences in PSA progression or death, and no differences in the rate of fractures and cardiovascular adverse events between degarelix and LHRH agonists). 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 to be a cost-effective use of NHS resources and concluded that degarelix could not be recommended for treating advanced hormone-dependent prostate cancer (that is, people with locally advanced or metastatic hormone-dependent prostate cancer).

4.21 The Committee noted comments received during consultation which highlighted that degarelix is particularly beneficial compared with LHRH agonists for older people, people with pre-existing cardiovascular disease, skeletal metastases, and impending ureteric and urethral obstruction, and that these subgroups should be considered. The Committee noted that the company did not include any cost-effectiveness 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.

4.22 The Committee considered the company's approach to including spinal cord compression events in the model, the ERG's exploratory analyses for the subgroup of patients with spinal metastases with impending or actual spinal cord compression. It heard from the clinical and patient experts that degarelix may be

beneficial for people with spinal metastases from the prostate who may develop spinal cord compression. The Committee noted that the clinical trials included in the company's submission reported only 1 spinal cord compression in the LHRH agonist group and that the company derived the rates of these events from Oh et al. (2010), as used in the model from Lu et al. (2011), for its economic model. The Committee noted the ERG's comment that because of the lack of data on the rate of spinal cord compression, this was the best available source of data for this adverse event, but also noted that the company did not consider a subgroup analysis for this population. The Committee noted that the company assumed in its model that only people having LHRH agonists could have spinal cord compression. The Committee understood the clinical plausibility behind this rationale, but it noted that this assumption would only be relevant for spinal cord compression that occurred as a result of the flare associated with starting treatment with LHRH agonists (see section 4.11). The Committee considered the ERG's exploratory analyses for people with spinal metastases with actual or impending spinal cord compression (see section 3.34). This was a subgroup specified in the scope, and it was assumed that people having degarelix would not have spinal cord compression. The Committee considered this assumption to be optimistic after hearing from the clinical experts that degarelix could reduce the incidence of spinal cord compression associated with testosterone flare, but that it would not prevent all spinal cord compression. Based on the assumption of equivalent efficacy in terms of PSA progression and overall survival between degarelix and LHRH agonists, the QALY gain for degarelix could be higher compared with triptorelin because degarelix does not produce an initial testosterone flare and so would reduce the risk of associated spinal cord compression. The Committee noted that the rate of spinal cord compression was unknown in this subgroup and that the ERG's

additional exploratory analysis, assuming different rates of spinal cord compression in people having LHRH agonists, showed that degarelix could potentially be considered cost effective compared with triptorelin in this subgroup. The Committee noted that this exploratory subgroup referred to people with actual or impending spinal cord compression. It also noted comments from clinical and patient experts that when people have actual or impending spinal cord compression (that is, when signs and symptoms of spinal cord compression are already present) treatment with degarelix would be considered to be too late, and degarelix would have limited clinical benefit at this stage in the disease process (see section 4.11). The Committee concluded that degarelix is not a treatment for spinal cord compression and it would have limited clinical impact in terms of avoiding spinal cord compression in people with spinal metastases from the prostate who already have signs and symptoms of spinal cord compression.

4.23 The Committee understood from the company and from the clinical and patient experts that degarelix is not a treatment for spinal cord compression but it would be considered most suitable for people with prostate cancer who have spinal metastases, because they may develop spinal cord compression. It also understood from the clinical experts that identifying people who may develop spinal cord compression directly as a result of a testosterone flare from the broader population of those with spinal metastases is very challenging. The Committee noted the Appeal Panel's conclusion that efforts should be made to accurately define the patient population if the technology is to be approved for a particular patient group, so that the NHS will be able to effectively operationalise such a decision. The Appeal Panel stated that the guidance should be precise in its language and noted that any term used must be clearly defined and consistently and exclusively used

to describe the group defined. The definition of the patient group should be very clear, not reliant on different interpretations of language, and capable of application in a routine clinical setting. The Committee accepted the views of the company, clinical and patient experts that a potential subgroup of people with spinal metastases from the prostate who may develop spinal cord compression as a result of testosterone flare may exist in clinical practice, and it discussed at length the ways in which this population could be identified and defined (see section 4.11). However, it concluded that this subgroup could not be reliably identified beyond those people who have spinal metastases from the prostate. The Committee expressed concerns that if this subgroup cannot be clearly identified and defined in clinical practice, degarelix is likely to be used in all people with spinal metastases. It noted that the company had not presented a cost-effectiveness analysis for this group and it was mindful that all of the ICERs presented for the overall population of people with locally advanced or metastatic hormone-dependent prostate cancer were outside the range normally considered to be a cost-effective use of NHS resources (see section 4.20). The Committee noted that it would have liked to consider an analysis specifically for people with spinal metastases from the prostate. The Committee agreed that if such an analysis showed that the ICERs for degarelix compared with LHRH agonists are considerably lower than the ICERs for the overall population with locally advanced or metastatic hormone-dependent prostate cancer, this would allow the Committee to reassess the cost effectiveness of degarelix treatment for all people with spinal metastases from the prostate (because it is not currently possible to identify those people with spinal metastases from the prostate who are most likely to develop spinal cord compression as a result of testosterone flare).

4.24 The Committee discussed the DSU's economic analysis that varied the rate of spinal cord compression in the model. The Committee noted that the DSU applied estimated rates of spinal cord compression that could be representative of the expected rate of spinal cord compression for the subgroup of people with spinal metastases from the prostate, who may develop spinal cord compression (see sections 3.57 and 3.58). The Committee noted that the DSU stated that these analyses should be interpreted with caution because of the uncertainty of the estimated rates and because they used the same model and assumptions from the economic analysis for the whole population with locally advanced or metastatic hormone-dependent prostate cancer, which may not be appropriate for the subgroup analyses. The Committee recalled its previous conclusion that the DSU estimated rate of spinal cord compression in people with spinal metastases from the prostate was subject to high uncertainty and it was not robust enough to use for decision-making in this subgroup (see section 4.12). The Committee also noted that all the analyses used some assumptions from the original model that were considered clinically uncertain or implausible: all patients having LHRH agonists had testosterone flare; spinal cord compression occurred solely as a result of testosterone flare; anti-androgen treatment with bicalutamide did not have an effect on reducing testosterone flare and thus reducing spinal cord compression; and no spinal cord compression occurred in patients having degarelix. The Committee noted that even when considering a model which incorporated all these assumptions degarelix could not be considered a cost-effective use of NHS resources unless the rate of spinal cord compression within 30 days of starting treatment with LHRH agonists is approximately 3% or higher. The Committee noted that the best evidence available showed that the estimated rate of spinal cord compression in people with metastatic prostate cancer was approximately 0.96%

and that this was confirmed by the clinical experts at the meeting. The Committee was aware that at a rate of spinal cord compression of 0.96%, the ICERs for degarelix compared with LHRH agonists in people with locally advanced or metastatic hormone-dependent prostate cancer were outside the range which is normally considered to be a cost-effective use of NHS resources (see section 4.20). The Committee concluded that, based on these considerations and the DSU's exploratory analyses degarelix could not be recommended for the whole population with locally advanced or metastatic hormone-dependent prostate cancer or in people with spinal metastases from the prostate.

4.25 The Committee discussed whether degarelix was innovative in its potential to make a significant and substantial impact on health-related benefits. The company noted that it considers degarelix to be a step-change in therapy from the current standard of care (LHRH agonists) because it provides more rapid and improved disease control, lower risk of disease progression, improved survival, no testosterone flare with initial treatment and fewer cardiovascular events. The company stated that all relevant health-related benefits were included in the QALY calculation. The Committee did not consider degarelix to be a step-change in managing advanced hormone-dependent prostate cancer. The Committee concluded that there were no additional QALYs associated with degarelix that had not been incorporated into the economic model and the cost-effectiveness estimates.

4.26 The Committee considered whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS Payment Mechanism, when appraising degarelix. The Committee noted NICE's position statement in this regard, and accepted the conclusion 'that the 2014 PPRS Payment Mechanism should not, as a matter of

course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard from the company that the list price of degarelix does not reflect any impact from the PPRS payment mechanism and that although this would have an effect on the cost of degarelix they did not know how large this impact would be. The Committee heard nothing substantial to suggest that there is any basis for taking a different view with regard to the relevance of the PPRS to this appraisal of degarelix. It therefore concluded that the PPRS Payment Mechanism was not relevant for its consideration of the cost effectiveness of degarelix.

Summary of Appraisal Committee's key conclusions

TAXXX	**Appraisal title: Degarelix for treating advanced hormone-dependent prostate cancer**	**Section**
Key conclusion		
Degarelix is not recommended within its marketing authorisation for treating advanced hormone-dependent prostate cancer.		1.1
The Committee concluded that degarelix was non-inferior to luteinising hormone-releasing hormone (LHRH) agonists in suppressing testosterone levels. It acknowledged that degarelix is beneficial for avoiding testosterone flare which is particularly important in people with spinal metastases, some of whom may develop spinal cord compression, because there may be a relationship between the testosterone flare when hormonal treatment starts and spinal cord compression.		4.6
The Committee noted that in the Evidence Review Group (ERG)'s additional exploratory analyses, the incremental cost-effectiveness		4.20

ratio (ICER) for degarelix compared with 3-monthly triptorelin was £103,200 per quality-adjusted life year (QALY) gained when the Committee's preferred assumptions of no differences in prostate-specific antigen (PSA) progression or death, and no differences in the rate of fractures and cardiovascular adverse events between degarelix and the LHRH agonists were 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 to be a cost-effective use of NHS resources and concluded that degarelix could not be recommended for treating advanced hormone-dependent prostate cancer (that is, people with locally advanced or metastatic hormone-dependent prostate cancer).	
The Committee heard from the clinical experts that there may be a relationship between the testosterone flare when hormonal treatment starts and spinal cord compression in people with spinal metastases from the prostate. The risk of spinal cord compression may be lower in people having degarelix compared with LHRH agonists because degarelix does not produce an initial flare in testosterone levels. The Committee heard from some of the patient and clinical experts that it would not be appropriate to wait until people present with signs and symptoms that could be suggestive of spinal cord compression to start degarelix, because it is not a treatment for spinal cord compression and any benefit would be limited at this stage in the disease process which would be too late for preventing the event to occur. The Committee concluded that it is not possible to reliably identify and precisely define a subgroup of patients who face a higher risk of developing spinal cord compression from the broader population of patients with spinal	4.11

metastases from the prostate. The Committee was aware that at a rate of spinal cord compression of 0.96%, the ICERs for degarelix compared with LHRH agonists in people with locally advanced or metastatic hormone-dependent prostate cancer were outside the range which is normally considered to be a cost-effective use of NHS resources The Committee also noted that the DSU estimated rate of spinal cord compression in people with spinal metastases from the prostate was subject to high uncertainty and it was not robust enough to use for decision-making in this subgroup. The Committee concluded that, based on these considerations and the DSU's exploratory analyses degarelix could not be recommended for the whole population with locally advanced or metastatic hormone-dependent prostate cancer or in people with spinal metastases from the prostate	4.24
Current practice	

Clinical need of patients, including the availability of alternative treatments	The Committee heard from the clinical experts that LHRH agonists (leuprorelin, goserelin and triptorelin) are first-line treatments for hormone-dependent prostate cancer and that clinicians consider each LHRH agonist to have equivalent clinical efficacy. The clinical experts also stated that, in clinical practice, treatment with LHRH agonists continues after the disease has progressed and until death. The Committee heard from the patient experts that advanced prostate cancer is a diverse disease and people respond differently to treatments, so the availability of a range of treatment options is important.	4.1 4.3
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee noted that the clinical experts highlighted that degarelix is particularly appropriate for people at high risk of disease progression (that is, with a PSA level of more than 20 ng/ml), older people, those with pre-existing cardiovascular disease, and people with spinal metastases (some of whom may go on to develop spinal cord compression). The Committee heard from the clinical experts that there may be a relationship between the testosterone flare when hormonal treatment starts and spinal cord	4.2 4.11

	compression in people with spinal metastases from the prostate. The risk may be lower in people having degarelix compared with LHRH agonists because degarelix does not produce an initial flare in testosterone levels. The Committee did not consider degarelix to be a step-change in managing advanced hormone-dependent prostate cancer. The Committee concluded that there were no additional QALYs associated with degarelix that had not been incorporated into the economic model and the cost-effectiveness estimates.	4.25
What is the position of the treatment in the pathway of care for the condition?	The Committee concluded that the likely position of degarelix in the treatment pathway is as first-line hormonal therapy for treating advanced hormone-dependent prostate cancer; that is, at the same point in the pathway as the LHRH agonists.	4.1
Adverse reactions	The most common adverse reactions with degarelix are related to the effects of testosterone suppression, including hot flushes and weight increase, or injection site reactions (such as pain and erythema).	2.2
Evidence for clinical effectiveness		
Availability, nature and quality of	The main source of evidence for the clinical effectiveness of degarelix compared with	4.5, 4.6

evidence	leuprorelin was the CS21 randomised controlled trial and the CS21A extension study. The Committee also considered the evidence presented by the company from randomised controlled trials of degarelix compared with other LHRH agonists (CS28, CS30, CS31, CS35 and CS37). The Committee noted that all 6 studies were open label, included patients at all stages of prostate cancer and were primarily designed as non-inferiority trials. The Committee noted that the company did not identify any head-to-head trial evidence comparing degarelix with bicalutamide monotherapy. The Committee concluded that, based on the available evidence and UK clinical practice, it supported the company's view that comparing degarelix with bicalutamide monotherapy was not appropriate. The Committee noted the NICE Decision Support Unit (DSU)'s work on the subgroup of people with metastatic hormone-dependent prostate cancer with spinal metastases from the prostate. The Committee concluded that the work presented by the DSU provided further confirmation of the fact that it is not possible to clearly identify and define a subgroup of people with spinal metastases from the	4.4 4.12

	prostate who may develop spinal cord compression as a result of a testosterone flare, and that the best evidence available for estimating the rate of spinal cord compression in people with metastatic hormone-dependent prostate cancer was the study by Oh et al. (2010).	
Relevance to general clinical practice in the NHS	The Committee heard from the clinical experts and the ERG that the clinical trials in the company's submission included populations and treatment regimens that were different to those seen in UK clinical practice. These included differences in the proportion of patients having treatment with bicalutamide for protection against testosterone flare, the inclusion of patients at all stages of prostate cancer and the use of unlicensed doses and regimens of degarelix in the trials. The Committee concluded that the generalisability of the trials' results to UK clinical practice was limited.	4.5
Uncertainties generated by the evidence	The Committee considered that the results for PSA progression and long-term PSA progression benefit for degarelix compared with LHRH agonists were highly uncertain. The Committee concluded that it was plausible to assume equivalent clinical efficacy between LHRH agonists, but there was a lack of robust evidence to support an overall survival benefit with degarelix	4.7 4.8

	compared with LHRH agonists.	
	The Committee concluded that there was a high degree of uncertainty about whether there was any difference in the rate of fractures for degarelix compared with the LHRH agonists.	4.9
	The Committee discussed in detail the clinical evidence presented for people with pre-existing cardiovascular disease. It concluded that, because of the uncertainty around both the pooled analyses and the meta-regression analyses presented by the company 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 compared with LHRH agonists.	4.10
	The Committee concluded that, although degarelix could offer particular benefit for people with spinal metastases who may develop spinal cord compression (because, unlike LHRH agonists, it does not produce an initial surge in testosterone levels, which is potentially associated with spinal cord compression), it is difficult to identify which people with spinal metastases would develop spinal cord compression directly as a result of the testosterone flare that can occur with	4.11

	LHRH agonists.	
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee heard from the clinical experts that there may be a relationship between the testosterone flare when hormonal treatment starts and spinal cord compression in people with spinal metastases from the prostate. The risk may be lower in people having degarelix compared with LHRH agonists because degarelix does not produce an initial flare in testosterone levels. The clinical experts acknowledged that degarelix is not a treatment for spinal cord compression but it may provide an additional clinical benefit for people with spinal metastases from the prostate, who may develop spinal cord compression. The experts also acknowledged that there is no evidence to support the use of degarelix in this subgroup beyond their experience in clinical practice. The Committee concluded that the work presented by the DSU provided further confirmation of the fact that it is not possible to clearly identify and define a subgroup of people with spinal metastases from the prostate who may develop spinal cord compression as a result of a testosterone flare.	4.11, 4.12
Estimate of the size of the clinical	The Committee concluded that degarelix was non-inferior to LHRH agonists in suppressing	4.6

effectiveness including strength of supporting evidence	testosterone levels and acknowledged that it is beneficial for avoiding testosterone flare. The Committee noted the post-hoc analyses of CS21 published by Tombal et al. (2010) that showed 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 not statistically significant. The Committee considered that the results for PSA progression and long-term PSA progression benefit for degarelix compared with LHRH agonists were highly uncertain. It concluded that no PSA progression benefit from degarelix compared with LHRH agonists could be assumed.	4.7
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee noted the company's de novo economic analysis that assessed the cost effectiveness of degarelix compared with goserelin plus short-term anti-androgen treatment with bicalutamide for treating advanced hormone-dependent prostate cancer. It also noted that the company included comparisons between degarelix and other LHRH agonists (leuprorelin and triptorelin plus short-term anti-androgen treatment with bicalutamide) in scenario analyses. The Committee discussed the	3.14, 4.13

	clinical-effectiveness data, the company's submission of additional evidence, and assumptions in the company's updated economic model, which were submitted in response to consultation. The Committee noted that clinical-effectiveness data for the model were derived from CS21, CS21A and CS35, and the data for adverse events were derived from the meta-regression analyses. The Committee discussed the DSU's economic analysis that varied the rate of spinal cord compression in the model for the whole population with locally advanced or metastatic hormone-dependent prostate cancer.	4.24
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee was aware that PSA progression was the main driver of disease progression in the model, but it concluded that a PSA progression benefit for degarelix compared with LHRH agonists was highly uncertain. The Committee concluded that the company's assumption of differential PSA progression for degarelix compared with LHRH agonists was not proven. The Committee acknowledged that there was no robust evidence to support any overall survival benefit for degarelix compared with LHRH agonists and concluded that no overall survival benefit for degarelix compared with LHRH agonists	4.14 4.15

	should have been assumed in the model. The Committee concluded that there was considerable uncertainty around the estimated differences in the rates of fractures and cardiovascular events for degarelix compared with LHRH agonists. Therefore, it would have been more appropriate to assume no differences for the rate of cardiovascular events and fractures between degarelix and LHRH agonists in the model.	4.16
	The Committee noted that the DSU's economic analysis, that varied the rate of spinal cord compression in the model for the whole population with locally advanced or metastatic hormone-dependent prostate cancer, used some assumptions from the original model that were considered clinically uncertain or implausible: all patients having LHRH agonists had testosterone flare; spinal cord compression occurred solely as a result of testosterone flare; anti-androgen treatment with bicalutamide did not have an effect on reducing testosterone flare and thus reducing spinal cord compression; and no spinal cord compression occurred in patients having degarelix.	4.24

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee discussed the updated utility values that were applied in the company's model and included in the submission of additional evidence in response to consultation. It noted that the company's updated model used the mapping algorithm from McKenzie and van der Pol (2009) which the Committee had agreed was the most appropriate method to transform health-related quality-of-life data into utility values at its first meeting. The Committee concluded that using the utility algorithm by McKenzie and van der Pol was an appropriate change to the model.	4.17
Are there specific groups of people for whom the technology is particularly cost effective?	The Committee understood from the company and from the clinical and patient experts that degarelix would be considered most suitable for people with prostate cancer who have spinal metastases, because they may develop spinal cord compression. The Committee accepted the views of the company, clinical and patient experts that a potential subgroup of people with spinal metastases who may develop spinal cord compression as a result of testosterone flare may exist in clinical practice, and it discussed at length the ways in which this population could be identified and defined. However, it concluded that this subgroup could not be reliably identified beyond those	4.23

	people who have spinal metastases from the prostate. The Committee discussed the DSU's economic analysis that varied the rate of spinal cord compression in the model for the whole population with locally advanced or metastatic hormone-dependent prostate cancer. The Committee noted that the DSU estimated rate of spinal cord compression in people with spinal metastases from the prostate was subject to high uncertainty and it was not robust enough to use for decision-making in this subgroup.	4.24
What are the key drivers of cost effectiveness?	The ERG noted that the cost-effectiveness results were most sensitive to the exclusion of spinal cord compression adverse events, the modelling of fracture rates, the assumption that PSA progression had an effect on overall survival in patients with metastatic disease, and the assumption of no difference in PSA progression between degarelix and the LHRH agonists. The Committee was aware that PSA progression was the main driver of disease progression in the model, but it concluded that a long-term PSA progression benefit for degarelix compared with LHRH agonists was highly uncertain.and not proven.	3.32 4.14

Most likely cost-effectiveness estimate (given as an ICER)	The Committee noted that in the ERG's additional analyses for people with locally advanced or metastatic hormone-dependent prostate cancer, the ICER for degarelix compared with 3-monthly triptorelin was £103,200 per QALY gained when its preferred assumptions 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 were 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.	4.20
Additional factors taken into account		
Patient access schemes (PPRS)	The Committee heard nothing substantial to suggest that there is any basis for taking a different view with regard to the relevance of the PPRS to this appraisal of degarelix. It therefore concluded that the PPRS Payment Mechanism was not relevant for its consideration of the cost effectiveness of degarelix.	
End-of-life considerations	Not applicable.	

Equalities considerations and social value judgements	NICE considers that the potential equality issues identified during the scoping process cannot be addressed within this technology appraisal because of the lack of data for the identified groups (people of African–Caribbean family origin and older people). It is not expected that the recommendations in this technology appraisal would have any adverse impact on people with the mentioned characteristics.	

5 Proposed recommendations for further research

5.1 Further research is recommended to resolve uncertainties about the clinical effectiveness of degarelix compared with LHRH agonists such as leuprorelin, goserelin and triptorelin for treating advanced hormone-dependent prostate cancer, particularly in subgroups of people with pre-existing cardiovascular disease, people with skeletal (including spinal) metastases and people with impending ureteric and urethral obstruction. Research should be planned as part of well-conducted randomised clinical trials.

6 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the NICE website.

Published

- Prostate cancer: diagnosis and treatment NICE guideline 175 (2014).

- Metastatic spinal cord compression: diagnosis and management of adults at risk of and with metastatic spinal cord compression. NICE guideline 75 (2008).
- Improving outcomes in urological cancers. Cancer service guidance (2002).

7 Proposed date for review of guidance

7.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Gary McVeigh
Chair, Appraisal Committee
May 2015

8 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Gary McVeigh (Chair)
Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Dr Andrew Black (Vice Chair)
General Practitioner, Mortimer Medical Practice, Herefordshire

Dr Graham Ash
Consultant in General Adult Psychiatry, Lancashire Care NHS Foundation Trust

Dr Aomesh Bhatt
Regulatory and Medical Affairs Director Europe and North America, Reckitt Benckiser

Professor David Bowen

Consultant Haematologist, Leeds Teaching Hospitals NHS Trust

Dr Ian Campbell

Honorary Consultant Physician, Llandough Hospital, Cardiff

Ms Tracey Cole

Lay Member

Dr Ian Davidson

Lecturer in Rehabilitation, University of Manchester

Professor Simon Dixon

Professor of Health Economics, University of Sheffield

Martin Duerden

Assistant Medical Director, Betsi Cadwaladr Health Board, North Wales

Dr Alexander Dyker

Consultant Physician, Wolfson Unit of Clinical Pharmacology, University of Newcastle

Susan Dutton

Senior Medical Statistician, Oxford Clinical Trials Research Unit

Christopher Earl

Surgical Care Practitioner, Wessex Neurological Centre at Southampton University Hospital

Gillian Ells

Prescribing Advisor – Commissioning, NHS Hastings and Rother and NHS East Sussex Downs and Weald

Professor Paula Ghaneh

Professor and Honorary Consultant Surgeon, University of Liverpool

Dr Susan Griffin

Research Fellow, Centre for Health Economics, University of York

Professor Carol Haigh

Professor in Nursing, Manchester Metropolitan University

Professor John Henderson

Professor of Paediatric Respiratory Medicine, University of Bristol and Bristol Royal Hospital for Children

Dr Paul Hepple

General Practitioner, Muirhouse Medical Group

Professor John Hutton

Professor of Health Economics, University of York

Professor Steven Julious

Professor in Medical Statistics, University of Sheffield

Dr Tim Kinnaird

Lead Interventional Cardiologist, University Hospital of Wales, Cardiff

Emily Lam

Lay member

Warren Linley BSc

Senior Research Fellow, Centre for Health Economics and Medicines Evaluation, Bangor University

Malcolm Oswald

Lay member

Dr Oluwafemi Oyebode

Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health

Dr John Radford

Director of Public Health, Rotherham Primary Care Trust and MBC

Dr Peter Selby

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Dr Mohit Sharma

Consultant in Public Health, Public Health England

Dr Peter Sims

GP, Devon

Dr Murray Smith

Associate Professor in Social Research in Medicines and Health, University of Nottingham

Cliff Snelling

Lay member

Guideline representatives

The following individuals, representing the Guideline Development Group responsible for developing NICE's clinical guideline related to this topic, were invited to attend the meeting to observe and to contribute as advisers to the Committee.

Dr Peter Kirkbride

Medical Director, Clatterbridge Cancer Centre, Clinical Lead

Dr John Graham

Director, National Collaborating Centre for Cancer

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Pilar Pinilla Dominguez
Technical Lead

Fay McCracken and Joanna Richardson
Technical Advisers

Kate Moore
Project Manager

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by the School of Health and Related Research (ScHARR):

- Uttley L, Whyte S, Gomersall T et al. Degarelix for treating advanced hormone-dependent prostate cancer: A single technology appraisal, October 2013

B. The Decision Support Unit (DSU) report for this appraisal was prepared by the School of Health and Related Research (ScHARR):

- Chambers D, Whyte S, Wong R, Degarelix for treating advanced hormone-dependent prostate cancer [id590] spinal cord compression associated with hormonal therapy in men with hormone-dependent metastatic prostate cancer: a systematic review and economic assessment, April 2015

C. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Ferring Pharmaceuticals

II. Professional/specialist and patient/carer groups:

- Prostate Cancer UK

- Tackle Prostate Cancer
- British Association of Urological Surgeons
- British Uro-Oncology Group
- Cancer Research UK
- Royal College of Nursing
- Royal College of Physicians
- Urology Foundation

III. Other consultees:

- Department of Health
- NHS Durham Dales, Easington and Sedgefield CCG
- NHS England
- NHS Southport and Formby CCG
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- AstraZeneca
- Bayer
- Ferring Pharmaceuticals
- Ipsen
- Orion Pharma K
- Sanofi
- National Cancer Research Network
- School of Health and Related Research (ScHARR)

- National Institute for Health Research Health Technology Assessment programme
- National Collaborating Centre for Cancer

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on degarelix by attending Committee discussions and providing written evidence to the Committee. They are invited to comment on the ACD.

- Dr Heather Payne, Consultant Clinical Oncologist, nominated by British Uro-Oncology Group – clinical expert
- Dr Isabel Syndikus, Consultant Clinical Oncologist, nominated by the Royal College of Physicians – clinical expert
- Bruce Turner, Uro-oncology Nurse Practitioner, nominated by Ferring Pharmaceuticals – clinical expert
- Dr Maria Vilarino-Varela, Consultant Clinical Oncologist, nominated by the British Uro-Oncology Group – clinical expert
- David Baxter-Smith, nominated by Tackle Prostate Cancer – patient expert
- Hugh Gunn, nominated by Tackle Prostate Cancer – patient expert
- Stuart Watson, nominated by Prostate Cancer UK – patient expert

D. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Ferring Pharmaceuticals