NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Degarelix for treating advanced hormone-dependent prostate cancer

This guidance was developed using the single technology appraisal (STA) process

1 Guidance

1.1 Degarelix is recommended as an option for treating advanced hormone-dependent prostate cancer, only in adults with spinal metastases who present with signs or symptoms of spinal cord compression.

1.2 People currently receiving treatment initiated within the NHS with degarelix that is not recommended for them by NICE in this guidance 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 (LHRH). 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 UK marketing authorisation 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' [BNF] edition 66). The manufacturer's estimate of a total course of treatment (including administration) is £12,306. The manufacturer estimated that, assuming treatment with degarelix continues until disease progression, the total time spent on treatment is 5.9 years (including time spent receiving 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 manufacturer's submission

The Appraisal Committee (section 8) considered evidence submitted by the manufacturer of degarelix and reviews of these submissions by the Evidence Review Group (ERG; section 9).

3.1 The manufacturer'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, conducted in the USA and Europe and were primarily designed to demonstrate that degarelix was non-inferior to LHRH agonists (that is, no worse than LHRH agonists) for treating hormone-dependent prostate cancer. Patients receiving LHRH agonists in the 6 trials also received 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 received 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 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 receiving 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 receiving leuprorelin ($p<0.0001$).The manufacturer 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 the 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 manufacturer 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 percentage points. The manufacturer 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 manufacturer 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 manufacturer 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 manufacturer stated that PSA progression is used routinely in clinical practice as a prognostic indicator to assess disease progression and/or 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 receiving the licensed dose of degarelix (240/80 mg), 85.8% (95% CI 79.8% to 90.1%) for patients receiving the unlicensed dose of degarelix (240/160 mg) and 85.9% (95% CI 79.9% to 90.2%) for patients receiving leuprorelin. The manufacturer 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 manufacturer 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 manufacturer conducted 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 had PSA progression respectively, 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 manufacturer 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 receiving 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 93.8–98.9) for degarelix and 95.1% (95% CI 90.7–97.4) for leuprorelin. These results showed that patients receiving degarelix had a lower risk of PSA progression or death compared with patients receiving leuprorelin (p=0.05). When adjusted for baseline PSA levels and disease stage the results were not statistically significant (HR 0.664 [95%CI 0.385 to 1.146]). The manufacturer 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 receiving degarelix and 4.9% (95% CI 2.6% to 9.3%) for patients receiving leuprorelin. The manufacturer 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 manufacturer included results from CS21A, the extension trial of CS21, in which all patients who had previously received 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 received a monthly degarelix maintenance dose of 80 mg. The manufacturer stated that there was sustained suppression of both testosterone and PSA levels with degarelix irrespective of whether patients received 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 manufacturer 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 people with metastatic prostate cancer was statistically significant between degarelix and leuprorelin at day 364 (p=0.014). The manufacturer 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 people with metastatic disease were suppressed to a greater extent throughout 1-year treatment with degarelix (p=0.0383).

3.10 The manufacturer 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 QLC-C30 (European Organization for Research and Treatment of Cancer, quality of life – C 30) questionnaires to obtain generic and cancer-specific measures of quality of life respectively. The manufacturer stated that all the SF12 v2 scores were comparable across treatment groups and study days 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 manufacturer conducted 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 manufacturer included data from CS21, CS28, CS30, CS31 and CS35. The results of the manufacturer's meta-analyses for these 2 end points showed that there was statistically significant heterogeneity between trials

based on I-squared estimates of 90.0% at week 4; 91% at week 8; and 81.4% at week 12 for the difference in the percentage change in PSA levels, and of 72.8% from day 28 to 84 and 91.6% from day 28 to 364 for the difference in the cumulative probability of testosterone levels of 0.5 ng/ml or less. The manufacturer 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 manufacturer 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 manufacturer 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 manufacturer 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 receiving degarelix compared with the group receiving LHRH agonists (weighted odds ratio [OR]: 0.48, 95% CI 0.25 to 0.91, p=0.025).

3.12 The manufacturer 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 manufacturer pooled data from 2328 patients: 1491 patients received degarelix and 837 received LHRH agonists

(goserelin: n=458; leuprorelin: n=379). Among the patients with pre-existing cardiovascular disease, the risk of cardiac events within 1 year of starting therapy was lower for patients receiving degarelix compared with those receiving LHRH agonists (HR 0.44, 95% CI 0.26 −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 receiving degarelix compared with patients receiving 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 manufacturer also referred to a study by Albertsen et al. (2013) in which the results of the pooled analysis for people with pre-existing cardiovascular disease were presented. The authors concluded that the study has several limitations, the findings should only be interpreted as hypothesis generating and randomised controlled trials will be needed to validate the observations and define the mechanism by which they occur.

3.13 The manufacturer carried out 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 manufacturer 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; CS31). The manufacturer 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 were statistically significant. The manufacturer stated that the lack of evidence to compare bicalutamide with degarelix prevented a robust comparison and that a naive indirect comparison was not carried out because it could provide misleading or biased estimates of treatment effects.

3.14 The manufacturer'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 manufacturer 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 manufacturer 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 received 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 manufacturer 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 manufacturer also conducted a subgroup analysis of patients with PSA levels greater than 20 ng/ml in CS21 because it suggested that these patients reflected the population receiving hormonal therapy in the UK more closely.

3.16 The manufacturer 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 and improved had the same utility as those whose spinal cord compression had resolved
- patients with metastatic disease whose disease 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 receive subsequent treatments depending on PSA progression.

The manufacturer 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 manufacturer investigated the fit of different parametric curves to the Kaplan-Meier data for patients receiving 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 manufacturer 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 manufacturer 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 Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen (NICE technology appraisal guidance 259). It was assumed that after anti-androgen withdrawal, all patients would have metastatic disease.

3.19 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 manufacturer 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 manufacturer generated separate survival curves for patients with metastatic disease and non-metastatic disease. In the model patients faced different risks of mortality as they progressed through each treatment. The manufacturer 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 manufacturer 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 manufacturer 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 manufacturer applied a reduced mortality risk to patients with metastatic disease receiving abiraterone based on NICE technology appraisal guidance 259. It also assumed a reduced mortality risk for patients receiving 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 manufacturer incorporated the rate of adverse events in the model and assumed that patients receiving degarelix and LHRH agonists could have fractures, joint-related signs and symptoms and cardiovascular events. In contrast, only patients receiving 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 manufacturer modelled musculoskeletal and cardiovascular events using parametric curves fitted to the pooled observations of the 6 randomised controlled trials included as clinical evidence. The manufacturer 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 manufacturer 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 manufacturer 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 manufacturer 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 needed to be treated for this condition until death. The manufacturer 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 manufacturer 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 from 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 manufacturer 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. The manufacturer carried out 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 manufacturer also carried out 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 manufacturer assumed that the unit costs for the monthly dose of leuprorelin (Prostap), goserelin (Zoladex) and triptorelin (Decapeptyl) were £75.24, £65 and £69 respectively, and assumed that the unit costs of 3-monthly leuprorelin, goserelin and triptorelin were £225.72, £235 and £207 respectively. The manufacturer 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 manufacturer also assumed that treatment initiation costs consisted of a CT and bone scan, a PSA test and an 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 manufacturer stated that all costs and resource use were validated by UK clinicians.

3.23 The results of the manufacturer'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 manufacturer also presented results for people with a high risk of disease progression (PSA levels at baseline greater than 20 ng/ml) and for people with cardiovascular disease at baseline. The results showed that for people with baseline PSA levels greater than 20 ng/ml, degarelix dominated goserelin, providing 0.59 additional QALYs and costing £1691 less than goserelin. For people 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 manufacturer conducted 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 manufacturer'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 manufacturer 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 manufacturer'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 manufacturer presented data on the clinical efficacy of degarelix based on clinical trials that included patients at 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 manufacturer'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 specialists who highlighted that most patients in the UK who

receive treatment with LHRH agonists will receive anti-androgen flare protection with bicalutamide and the proportion of patients who received anti-androgen flare protection in the trials was low.

3.25 The ERG noted that the manufacturer 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 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 manufacturer's submission (see section 3.12) were inappropriate and should be interpreted with caution.

3.26 The ERG considered the meta-analyses conducted by the manufacturer. It noted that the manufacturer did not sufficiently justify the assumption that leuprorelin and goserelin had equivalent efficacy. Furthermore, the results for PSA response showed significant heterogeneity, but the manufacturer did not carry out a formal meta-regression in the orginal submission. The ERG noted that the manufacturer 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 manufacturer comparing degarelix with the LHRH agonists (goserelin, leuprorelin and triptorelin) and with bicalutamide. The ERG noted the manufacturer'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 carried out a revised mixed treatment comparison using 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% CrI 0.07 to 0.95).

3.29 The ERG considered the different assumptions applied in the manufacturer's original economic model. It noted the assumption that patients receive 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 does not need to be 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 manufacturer did not include any randomised controlled trials that directly compared degarelix with bicalutamide, an indirect comparison could have been conducted. The ERG further noted that the benefit of degarelix compared with the 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 specialists 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 specialists 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 manufacturer'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 manufacturer's model structure.

3.31 The ERG noted that the results of the manufacturer'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 manufacturer's assumption that the rate of fractures increased over time for people receiving LHRH agonists and decreased over time for people receiving degarelix. The ERG suggested that, based on advice from clinical specialists, 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 manufacturer's economic model had several limitations. The ERG carried out additional analyses and presented an updated treatment pathway based on expert opinion, which it used in its exploratory analyses. The ERG´s 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 receiving chemotherapy after PSA progression would be 70% and the proportion of patients receiving abiraterone would be 70%.

The results of the ERG's scenario 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 conducted 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 the LHRH agonists. The ICER for degarelix when equivalent efficacy of degarelix and the LHRH agonists was assumed 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 conducted an additional exploratory analysis, correcting for an implementation error in the manufacturer's model, and assumed:

- treatment with degarelix and LHRH agonists would continue until death, in line with clinical practice and their licensed indications
- no differential treatment effect of degarelix compared with LHRH agonists in terms of PSA progression or death
- the proportion of patients receiving chemotherapy after PSA progression would be 70% and the proportion of patients receiving abiraterone would be 70%
- the same rate of fractures for people receiving degarelix and LHRH agonists
- the same rate of cardiovascular events for people receiving degarelix and 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 undertook 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 receiving 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 was higher compared with triptorelin because of the lower utility decrement associated with spinal cord compression. The ERG concluded that if the rate of spinal cord compression in this subgroup was higher than 3.5%, degarelix would be dominant compared with triptorelin (that is, less costly and more effective).

Manufacturer's submission of additional evidence

3.35 The manufacturer submitted additional evidence in response to consultation. It provided further clarification on PSA progression efficacy data, cardiovascular event data and subgroups for whom degarelix offers greatest benefit. The manufacturer 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 manufacturer incorporated the results from the meta-regression analyses, the updated treatment pathway and updated utility values into the economic model and presented updated cost-effectiveness results including 2 new base cases; an updated base case and a manufacturer's conservative base case.

3.36 The manufacturer restated the mechanism of action of degarelix and 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 manufacturer 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 receiving leuprorelin to degarelix, and 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 manufacturer 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 manufacturer stated that LHRH agonists are associated with destabilisation of established vascular lesions and primarily 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 manufacturer conducted non-stratified one-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 conducted 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 >20 ng/ml population)
- risk of fractures (using data from CS21, CS35, and CS37).

All data from the group of patients who received 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 people 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 manufacturer and therefore cannot be reported here). The manufacturer also applied updated parametric curve fits for PSA progression to address concerns about using data over different durations from the 2 trials and chose a log-normal distribution as the best fit. For each data set the manufacturer fitted 1 curve to the 5-year long-term data and 1 curve to the first year of data only.

3.40 The manufacturer carried out meta-regression analyses for serious cardiovascular adverse events (which included 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, body mass index and testosterone. The results of the meta-regression analyses showed a statistically significant decrease in the risk of serious cardiovascular adverse events, both including and excluding death within 1 year of starting therapy, for degarelix compared with LHRH agonists (the hazard ratio and confidence intervals for the risk of serious cardiovascular adverse events were marked as commercial in confidence by the manufacturer and therefore cannot be reported here).

3.41 The results of the manufacturer's meta-regression analyses for joint-related signs and symptoms showed a statistically significant decrease in the risk of joint-related signs and symptoms in the overall population for degarelix compared with LHRH agonists, but this result was not statistically significant for people 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 manufacturer and therefore cannot be reported here).

3.42 The results of the manufacturer's meta-regression analyses for fractures did not show statistically significant differences between degarelix and LHRH agonists for people with PSA levels of more than 20 ng/ml at baseline. The manufacturer noted that a proportional hazards assumption between the 2 treatment groups had been assumed in the original submission. However the manufacturer stated that this is unlikely to hold because in 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 it incorporated a scenario analysis in which the risk of fractures was increased for people receiving degarelix to give an equal risk of fractures between degarelix and LHRH agonists from year 2 onwards. The manufacturer noted that patients receiving either degarelix or LHRH agonists have an increased risk of fractures over time and therefore, the curves for fracture rate are likely to either stop separating or converge.

3.43 The manufacturer presented updated utility values based on the Committee's preferred mapping algorithm by McKenzie and van der Pol (2009). The manufacturer also noted the Committee's concerns about the possibility of double counting the impact of adverse events on health-related quality of life. It amended the utility values for people not experiencing an adverse event by PSA progression status to ensure there was no double counting for adverse events in the model.

3.44 The manufacturer presented an updated economic model which included the following changes:

- inclusion of the results from the one-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 in the treatment pathway
- 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.

3.45 The results of the manufacturer'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 those people 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 manufacturer also included a subgroup analysis for those people 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 manufacturer 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 of degarelix compared with LHRH agonists in reducing the risk of fractures (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 people 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 people 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 manufacturer's submission of additional evidence

3.47 The ERG reviewed and critiqued the manufacturer's submission of additional evidence. Overall, the ERG considered that the manufacturer's additional evidence was not based on robust analyses and suggested that the results presented in the 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 mechanisms of action of degarelix and the causal conclusions of the manufacturer'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 therefore it was not possible to support the manufacturer's claim of a statistically significant difference in PSA progression-free survival for degarelix compared with LHRH agonists.

3.49 The ERG discussed the manufacturer's meta-regression analyses for PSA progression-free survival, cardiovascular events, joint-related signs and symptoms and risk of fractures. It noted that the manufacturer used non-stratified one-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 re-stated that including CS35 in the analyses was not appropriate because it included an unlicensed dose of degarelix (see section 3.26). It

noted that although the manufacturer stated that there was no heterogeneity between the trials in the meta-regression analyses for all outcomes, this had not been appropriately assessed. The ERG stated that the interaction between trial and treatment had been adjusted together with several baseline covariates in the manufacturer's meta-regression analyses, and including other covariates could explain the heterogeneity in treatment across trials. The ERG considered that because CS21 and CS35 used different doses of degarelix, the random-effects model would have been more appropriate to detect clinical heterogeneity between trials. The ERG further noted that the manufacturer's analyses assumed that the estimated parameters were normally distributed in the probabilistic sensitivity analysis. The manufacturer fitted parametric distributions to pooled data, but it was not clear whether all included studies were homogeneous. The ERG also stated that it was unclear whether the 2 groups of patients in CS21 (receiving the licensed and unlicensed doses) were included in the meta-regression analyses. The ERG concluded that the manufacturer's meta-regression analyses were subject to several limitations.

3.50 The ERG considered the results of the meta-regression analyses for PSA progression-free survival in which data from CS21 and CS35 were combined. The ERG noted that it was not clear whether the definition of PSA progression-free survival was the same in CS21 and CS35 and therefore considered that it was not appropriate to combine both trials in the analyses. The ERG noted that for PSA progression-free survival, although the adjusted hazard ratio from the meta-regression analyses was statistically significant for degarelix compared with LHRH agonists in the overall population, it was not significant for people with PSA of more than 20 ng/ml at baseline and for people 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 manufacturer 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 people with PSA of more than 20 ng/ml at baseline than the observed hazard ratio is misleading because the manufacturer had already adjusted for baseline risk. The ERG concluded that the manufacturer'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 manufacturer'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 precise pooled estimate than it should be.

3.52 The ERG reviewed the changes to the manufacturer'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 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 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 within the manufacturer's original model that persisted in the updated model. It noted that the conservative base-case scenario in which the manufacturer assumed that the risk of fractures was equal for degarelix and LHRH agonists actually excluded fractures from the model for both treatment groups. The ERG also highlighted that the manufacturer did not present a subgroup analysis for people with pre-existing cardiovascular disease. Overall the ERG considered that the manufacturer'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.

3.53 Full details of all the evidence are in the manufacturer's submission and the ERG report.

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of degarelix, having considered evidence on the nature of advanced hormone-dependent prostate cancer and the value placed on the benefits of degarelix by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.2 The Committee discussed the current management of advanced hormone-dependent prostate cancer. It heard from the clinical specialists that luteinising hormone-releasing hormone (LHRH) agonists (leuprorelin, goserelin and triptorelin) are first-line treatments for hormone-dependent prostate cancer. Furthermore, clinicians consider each LHRH agonist to have equivalent clinical efficacy. The clinical specialists also stated that, in clinical practice, treatment with LHRH agonists continues after the disease progresses until death. The clinical specialists noted that the treatment pathway for people with advanced prostate cancer is changing; hormonal treatment is being given earlier, drugs such as enzalutamide and abiraterone are used after disease progression, and treatment with abiraterone is increasingly being considered before chemotherapy in the treatment pathway. The Committee noted the updated treatment pathway presented by the manufacturer in the submission of additional evidence, in which abiraterone is positioned before docetaxel and enzalutamide is introduced before chemotherapy and abiraterone. The Committee understood that although there may be variation in clinical practice, the updated treatment pathway presented by the manufacturer is not consistent with current NICE guidance (NICE technology appraisal 259 on Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen and NICE Technology appraisal in preparation of enzalutamide for treating metastatic hormone relapsed prostate cancer previously treated with a docetaxel-containing regimen). The Committee heard from the clinical specialists that the appropriate place for degarelix in the treatment pathway is as an alternative to the LHRH agonists. The Committee noted comments from consultation that indicated the usefulness of having guidance for ongoing treatment with hormonal therapy once testosterone

levels have been supressed to castration levels with degarelix and the possibility of switching to LHRH agonists after that in the interests of cost savings. 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. The clinical specialists also highlighted that degarelix is particularly appropriate for people at high risk of disease progression (that is, with a prostate-specific antigen [PSA] level of more than 20 ng/ml), for people with spinal metastases who present with signs or symptoms of spinal cord compression, older people and those with pre-existing cardiovascular disease. The Committee acknowledged that NICE clinical guideline 75 on metastatic spinal cord compression: diagnosis and management of adults at risk of and with 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 and neurological symptoms as radicular pain, any limb weakness, difficulty in walking, sensory loss, or bladder or bowel dysfunction. It also states that where a patient with prior diagnosis of cancer has neurological symptoms or signs suggestive of metastatic spinal cord compression, a magnetic resonance imaging (MRI) 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 specialists and included in the scope for

the appraisal, particularly to people with spinal metastases who present with signs or symptoms of spinal cord compression. It acknowledged that avoidance of testosterone flare is particularly beneficial for people who present with signs or symptoms of spinal cord compression and that degarelix may lower the risk of testosterone flare because it does not produce an initial surge in testosterone levels.

4.3 The Committee heard from the patient experts that patients 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, and 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 patients 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 subcutaneous administration of the LHRH agonists 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 manufacturer's submission. It noted that the appraisal scope listed bicalutamide monotherapy as a comparator, but this comparison was not included in the manufacturer’s submission. The Committee noted that the manufacturer did not identify any head-to-head trial evidence comparing degarelix with bicalutamide monotherapy. It

noted the ERG's comment that it may have been possible to conduct a naive indirect comparison. The Committee heard from the clinical specialists 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 people 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 manufacturer'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 manufacturer from randomised controlled trials of degarelix compared with other LHRH agonists (CS28, CS30, CS31, CS35 and CS37). It heard from the clinical specialists and the ERG that in clinical practice, people receiving hormonal therapy with LHRH agonists also receive 28 days treatment with bicalutamide for protection against testosterone flare. The Committee noted that in CS21 only 11% of patients in the leuprorelin group received 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 at all stages of prostate cancer, and that a large proportion of these patients had non-classifiable prostate cancer (approximately 19% of the patients in CS21). The Committee also noted that some of the trials included in the manufacturer'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 manufacturer'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 which is particularly important in people with spinal metastases who present with signs or symptoms of spinal cord compression because of the known relationship between the testosterone flare when hormonal treatment starts and the risk of spinal cord compression.

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) showing a statistically significant difference between degarelix and leuprorelin for PSA progression or death, but when adjusted for baseline PSA levels and disease stage, this difference was no longer statistically significant (see section 3.6). The Committee heard from the clinical specialists 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 results from the CS21A extension trial and that the manufacturer stated in the submission of additional evidence that the results of this study supported the statistically significant difference in PSA progression-free survival between degarelix and leuprorelin (see section 3.35). It also noted the ERG's comment that this difference between degarelix and leuprorelin was not demonstrated in CS21A because this trial did not include a comparator arm and all patients switched from leuprorelin to degarelix (see section 3.48). The Committee also noted the results of the manufacturer's pooled analyses from the manufacturer'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 manufacturer'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 manufacturer'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 overall the point estimate would be expected to be similar in both models, the random-effects model assumes that each trial may estimate

different treatment effects so the observed variation is likely to be higher than for the fixed-effects model, because it includes both the sampling error and an estimation of the heterogeneity of the trials. The fixed-effects model assumes that all trials estimate the same treatment effect and any observed variation is simply the result of sampling error. It noted that the random-effects model gives a truer estimate of the underlying variability than the fixed-effects model when there is heterogeneity between trials. The Committee noted that the trials included in the 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. It also noted that the ERG stated that the manufacturer had already adjusted for baseline risk. The Committee concluded that the results for PSA progression and long-term PSA progression benefit for degarelix compared with LHRH agonists were highly uncertain and therefore no PSA progression benefit from degarelix compared with LHRH agonists could be assumed.

4.8 The Committee discussed the results of the manufacturer'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 manufacturer'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 manufacturer's conclusion that the results showed equivalent clinical efficacy between LHRH agonists. The Committee heard from the clinical specialists 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 manufacturer'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 manufacturer's submission of additional evidence. The Committee noted the ERG's concerns about the robustness of the pooled analyses and the limitations of the manufacturer's meta-regression analyses (see section 3.49). The Committee noted that the manufacturer acknowledged that the rate of fractures is likely to increase in people receiving 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 manufacturer 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 specialists 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 specialists that the duration of the trials was not long enough to demonstrate changes in bone mineral density and therefore, these results should be considered as exploratory. 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 and therefore no difference between fracture rates could be assumed between treatment groups.

4.10 The Committee considered the results of the manufacturer's pooled analysis from its original submission, and the meta-regression analyses for cardiovascular events that were presented in the manufacturer'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 manufacturer'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 having a cardiovascular event with degarelix compared with LHRH agonists in people with pre-existing cardiovascular disease (see section

3.12). The Committee noted the comments received during consultation and the views of the clinical specialists, that degarelix may be particularly beneficial for people with pre-existing cardiovascular disease because 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 heard that the increase in conventional cardiovascular risk factors was due to androgen deprivation and was aware that degarelix, used within its licensed indication, 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 manufacturer's analysis included a very broad composite outcome of several cardiovascular conditions (myocardial infarction, ischaemic cerebrovascular conditions, haemorrhagic cerebrovascular conditions, embolic and thrombotic events, and other ischaemic heart disease). It was also aware that cardiovascular events were reported as adverse events in the study, and were not independent study end points. Furthermore, the patients included in this analysis were a subgroup of a subgroup and this reduced the power and robustness of the analysis and conclusions. The Committee was aware that Albertsen et al. concluded that their study has several limitations, the findings should only be interpreted as hypothesis generating and that randomised controlled trials will be needed to validate the observations and define the mechanism by which they occur. The Committee heard from the manufacturer 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, and these include suppression of both luteinising hormone and follicle-stimulating

hormone and the potential effect of degarelix in 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. The Committee discussed in detail the clinical evidence presented for this subgroup and concluded that because of the uncertainty around both the pooled analyses and the meta-regression analyses presented by the manufacturer and the lack of robust evidence confirming the effect of degarelix on reducing the risk of cardiovascular events compared with LHRH agonists, it was not possible to conclude that degarelix would reduce the risk of cardiovascular events in people with pre-existing cardiovascular disease compared with LHRH agonists.

4.11 The Committee heard from the clinical specialists that there is a relationship between the testosterone surge when hormonal treatment starts and the risk of spinal cord compression in people with spinal metastases. The risk may be lower in people receiving degarelix compared with LHRH agonists because degarelix does not produce an initial surge in testosterone levels. The clinical specialists agreed that degarelix provided an additional clinical benefit for the small subgroup of people with spinal metastases who present with signs or symptoms of spinal cord compression. The Committee noted the comments received during consultation outlining the benefits of degarelix compared with LHRH agonists for people with spinal metastases who present with signs or symptoms of spinal cord compression. Therefore, it concluded that degarelix may offer potential benefit for this subgroup because degarelix does not produce an initial surge in testosterone levels associated with spinal cord compression in people with spinal metastases.

Cost effectiveness

4.12 The Committee discussed the clinical and cost-effectiveness evidence presented in both the manufacturer's original submission and the submission of additional evidence which was submitted in response to consultation (see section 3.35). 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 (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.

4.13 The Committee discussed the clinical-effectiveness data for PSA progression used in the manufacturer'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 manufacturer's assumption of differential PSA progression for degarelix compared with LHRH agonists was not proven.

4.14 The Committee considered the manufacturer's assumption of a link between PSA progression on first-line treatment and an increased risk of mortality for patients 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 specialists 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.

4.15 The Committee noted that the results of the manufacturer's meta-regression analyses for fractures, joint-related signs and symptoms and cardiovascular events were used in the economic model. It was aware these analyses lacked robustness and that there was a high degree of uncertainty around these results (see sections 4.9 and 4.10). It noted that the results of the manufacturer'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 manufacturer'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.

4.16 The Committee discussed the updated utility values that were applied in the manufacturer's model and included in the submission of additional evidence in response to consultation. It noted that the manufacturer'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. algorithm used in the manufacturer's original model, it had been validated by external data sources 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.

4.17 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).

4.18 The Committee discussed the manufacturer's updated cost-effectiveness results from the economic model. It noted that in the manufacturer's submission of additional evidence in response to consultation, a probabilistic estimate of the ICER, 2 base-case scenarios (an updated base-case and the manufacturer's conservative base-case) and cost-effectiveness estimates for different subgroups were presented (see sections 3.45 and 3.46). The Committee noted that in the manufacturer's updated base-case analysis for degarelix compared with LHRH agonists, the ICER was £2730 per QALY gained. It noted that these results were still based on assumptions of greater clinical efficacy in terms of PSA progression, overall survival, reduction in rates of fracture during the first 2 years and reduction of cardiovascular events with degarelix compared with LHRH agonists. It noted its earlier conclusions that the evidence informing these assumptions was considered to be subject to a high degree of uncertainty. The Committee also noted the comments from the ERG that in the manufacturer's conservative base-case analysis, the manufacturer 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 manufacturer's conservative base-case was not appropriate for decision-making. The Committee concluded that the manufacturer's updated base-case ICER was still based on assumptions that were not plausible and was likely to underestimate the true incremental cost per QALY gained of degarelix compared with LHRH agonists.

4.19 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 specialists 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 specialists opinion on 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 4.14). It therefore concluded that no differences in PSA progression or death should be assumed in the model. The Committee considered, based on the clinical specialists' statements and the ERG comments, that the proportion of people who would receive 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 big 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, as per the ERG's additional exploratory analyses, the ICER for degarelix compared with 3-monthly triptorelin was £103,200 per QALY gained when its

preferred assumption of no differences in PSA progression or death, and no differences in the rate of fractures and cardiovascular adverse events between degarelix and the LHRH agonists was applied. It also noted that the ICERs for degarelix when other LHRH agonists were considered ranged from £70,600 per QALY gained compared with monthly triptorelin to £105,400 per QALY gained compared with 6-monthly triptorelin. The Committee noted that all ICERs were outside the range normally considered as a cost-effective use of NHS resources and concluded that degarelix could not be recommended for treating advanced hormone-dependent prostate cancer.

4.20 The Committee noted comments from consultation highlighting that degarelix is particularly beneficial compared with LHRH agonists for people with pre-existing cardiovascular disease, people with skeletal metastases and people with impending ureteric and urethral obstruction, and these subgroups should be considered. The Committee noted that the manufacturer 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.

4.21 The Committee considered the manufacturer's approach for including spinal cord compression events in the model and 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 specialists and patient experts that degarelix may be beneficial for people with spinal metastases who present with signs or symptoms of spinal cord compression. The Committee noted that the clinical trials included in the manufacturer's submission did not report any spinal cord

compression and that the manufacturer 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 manufacturer did not consider a subgroup analysis for this population. The Committee noted that the manufacturer assumed in the model that only people receiving LHRH agonists could have spinal cord compression and understood the clinical plausibility behind this rationale (see section 4.11). The Committee heard from the clinical specialists that degarelix could reduce the incidence of spinal cord compression associated with testosterone flare, but would not prevent all spinal cord compression. The Committee considered the ERG's exploratory analyses for people with spinal metastases with actual or impending spinal cord compression. This was a subgroup specified in the scope, and it was assumed that people receiving degarelix would not have 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 was higher compared with triptorelin because degarelix does not produce an initial testosterone flare and therefore, it would reduce the risk of spinal cord compression associated with this. 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 receiving LHRH agonists showed that degarelix was cost effective compared with triptorelin (see section 3.34). On balance, the Committee concluded that based on comments from the clinical specialists and patient experts, who noted that degarelix provided an important benefit for

people with spinal metastases who present with signs or symptoms of spinal cord compression (because degarelix does not produce an initial surge in testosterone levels associated with spinal cord compression), for which there are no treatments available, and the ERG's exploratory analysis, degarelix was a cost-effective use of NHS resources. The Committee therefore recommended degarelix as an option for treating advanced hormone-dependent prostate cancer only for people with spinal metastases who present with signs or symptoms of spinal cord compression.

4.22 The Committee discussed whether degarelix was innovative in its potential to make a significant and substantial impact on health-related benefits. The manufacturer 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 manufacturer 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.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Degarelix for treating advanced hormone-dependent prostate cancer	Section
Key conclusion		
Degarelix is recommended as an option for treating advanced hormone-dependent prostate cancer, only in people with spinal metastases who present with signs or symptoms of spinal cord compression. The Committee concluded that degarelix was non-inferior to LHRH agonists		1.1

in suppressing testosterone levels and acknowledged that it is beneficial for avoiding testosterone flare which is particularly important in people with spinal metastases who present with signs or symptoms of spinal cord compression because of the known relationship between the testosterone flare when hormonal treatment starts and the risk of spinal cord compression.	4.6
The Committee noted that, as per the ERG's additional exploratory analyses, the ICER for degarelix compared with 3-monthly triptorelin was £103,200 per QALY gained when the Committee's 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. The Committee noted that all ICERs were outside the range normally considered as a cost-effective use of NHS resources and concluded that degarelix could not be recommended for treating advanced hormone-dependent prostate cancer.	4.19
The Committee noted the ERG's exploratory analyses for people with spinal metastases and actual or impending spinal cord compression that assumed that based on equivalent efficacy in terms of PSA progression and overall survival between degarelix and LHRH agonists, the QALY gain for degarelix was higher compared with triptorelin because degarelix does not produce an initial testosterone flare it would reduce the risk of spinal cord compression associated with this. 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 receiving LHRH agonists showed that degarelix was cost effective compared with triptorelin. On balance, the Committee concluded that based on comments from the clinical specialists and patient experts, who noted that degarelix provided an important benefit for people with spinal metastases who present with signs or symptoms of spinal cord compression (because degarelix does not produce an initial surge in testosterone levels associated with spinal cord compression), for which there are no treatments available, and the ERG's additional exploratory analysis, degarelix was a cost-effective use of NHS resources. The Committee therefore recommended degarelix as an option for treating advanced hormone-dependent prostate cancer only for people with spinal metastases who present with signs or symptoms of spinal cord compression.	4.21

Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee heard from the clinical specialists 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 specialists also stated that, in clinical practice, treatment with LHRH agonists continues after the disease progresses until death. The clinical specialists noted that the treatment pathway for people with advanced prostate cancer is changing; hormonal treatment is being given earlier, drugs such as enzalutamide and abiraterone are used after disease progression, and treatment with abiraterone is increasingly being considered before chemotherapy in the treatment pathway.	4.2
	The Committee heard from patient experts that advanced prostate cancer is a diverse disease and people respond differently to treatments, and so the availability of a range of treatment options is important.	4.3
	The Committee heard from the clinical specialists and patient experts that degarelix provided an important benefit for people with spinal metastases who present with signs or symptoms of spinal cord compression because degarelix does not produce an initial surge in testosterone levels associated with spinal cord compression, for which there are no treatments available.	4.21

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 specialists highlighted that degarelix is particularly appropriate for people at high risk of disease progression (that is, with a prostate-specific antigen [PSA] level of more than 20 ng/ml), for people with spinal metastases who present with signs or symptoms of spinal cord compression, older people and those with pre-existing cardiovascular disease. The Committee heard from the clinical specialists that there is a relationship between testosterone surge when hormonal treatment starts and the risk of spinal cord compression in people with spinal metastases. This risk may be lower in people receiving degarelix compared with LHRH agonists because degarelix does not produce an initial surge in testosterone levels. The clinical experts agreed that degarelix provided an additional clinical benefit for the small subgroup of people with spinal metastases who present with signs or symptoms of spinal cord compression. The Committee noted the comments received during consultation on the appraisal consultation document outlining the benefit from degarelix compared with LHRH agonists for people with spinal metastases who present with signs or symptoms of spinal cord compression. Therefore, it concluded that degarelix may offer potential benefit for this subgroup because degarelix does not produce an initial surge in testosterone levels associated with spinal cord compression in people with spinal metastases. 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.	4.2 4.11 4.22
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.	4.2

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 evidence	The main source of evidence for the clinical effectiveness of degarelix compared with leuprorelin was the CS21 randomised controlled trial and the CS21A extension study. The Committee also considered the evidence presented by the manufacturer 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 manufacturer did not identify any head-to-head trial evidence comparing degarelix with bicalutamide monotherapy. The Committee heard from the clinical specialists 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 people 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 manufacturer's view that comparing degarelix with bicalutamide monotherapy was not appropriate.	4.5, 4.6 4.4
Relevance to general clinical practice in the NHS	The Committee heard from the clinical specialists and the ERG that there were differences between the clinical trials included in the manufacturer's submission and people receiving hormonal therapy in UK clinical practice. These included differences in the proportion of patients receiving 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 concluded that the results for PSA progression and long-term PSA progression benefit for degarelix compared with LHRH agonists were highly uncertain and therefore no PSA progression benefit from degarelix compared with LHRH agonists could be assumed. 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. 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. 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 manufacturer and the lack of robust evidence confirming the effect of degarelix on reducing the risk of cardiovascular events compared with LHRH agonists, it was not possible to conclude that degarelix would reduce the risk of cardiovascular events compared with LHRH agonists.	4.7 4.8 4.9 4.10
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee heard from the clinical specialists that there is a relationship between the testosterone surge when hormonal treatment starts and the risk of spinal cord compression in people with spinal metastases. The risk may be lower in people receiving degarelix compared with LHRH agonists because degarelix does not produce an initial surge in testosterone levels. The clinical specialists agreed that degarelix provided an additional clinical benefit for the small subgroup of people with spinal metastases who present with signs or symptoms of spinal cord compression. The Committee noted the comments received during consultation outlining the benefits of degarelix compared with LHRH agonists for people with spinal metastases who present with signs or symptoms of spinal cord compression. Therefore, it concluded that degarelix may offer potential benefit for this subgroup because degarelix does not produce an initial surge in testosterone levels associated with spinal cord	4.11

	compression in people with spinal metastases.	
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee 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. The Committee concluded that degarelix was non-inferior to LHRH agonists in suppressing testosterone levels and acknowledged that it is beneficial for avoiding testosterone flare which is particularly important in people with spinal metastases who present with signs or symptoms of spinal cord compression because of the known relationship between the testosterone flare when hormonal treatment starts and the risk of spinal cord compression.	4.6
	The Committee noted the post-hoc analyses of CS21 published by Tombal et al. (2010) showing a statistically significant difference between degarelix and leuprorelin for PSA progression or death, but when adjusted for baseline PSA levels and disease stage, this difference was not statistically significant. The Committee heard from the clinical specialists 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 concluded that the results for PSA progression and long-term PSA progression benefit for degarelix compared with LHRH agonists were highly uncertain and therefore no PSA progression benefit from degarelix compared with LHRH agonists could be assumed.	4.7

Evidence for cost effectiveness		
Availability and nature of evidence	The Committee noted the manufacturer'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 manufacturer 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 clinical-effectiveness data, the manufacturer's submission of additional evidence, and assumptions in the manufacturer'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.	3.14, 4.12
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 manufacturer'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 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.	4.13 4.14 4.15

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 manufacturer's model and included in the submission of additional evidence in response to consultation. It noted that the manufacturer'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.	4.16
Are there specific groups of people for whom the technology is particularly cost effective?	The Committee concluded that based on comments from the clinical specialists and patient experts, who noted that degarelix provided an important benefit for people with spinal metastases who present with signs or symptoms of spinal cord compression (because degarelix does not produce an initial surge in testosterone levels associated with spinal cord compression), for which there are no treatments available, and the ERG's exploratory analysis, degarelix was a cost-effective use of NHS resources. The Committee therefore recommended degarelix as an option for treating advanced hormone-dependent prostate cancer only for people with spinal metastases who present with signs or symptoms of spinal cord compression.	4.21
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. The Committee concluded that the manufacturer's assumption of differential PSA progression for degarelix compared with LHRH agonists was not proven.	3.32 4.13

Most likely cost-effectiveness estimate (given as an ICER)	The Committee noted that, as per the ERG's additional analyses, 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 was applied. It also noted that the ICERs for degarelix when other LHRH agonists were considered ranged from £70,600 per QALY gained compared with monthly triptorelin to £105,400 per QALY gained compared with 6-monthly triptorelin. The Committee noted that the rate of spinal cord compression was unknown in the subgroup of people with spinal metastases who present with signs or symptoms of spinal cord compression and that the ERG additional exploratory analysis assuming different rates of spinal cord compression in people receiving LHRH agonists showed that degarelix was cost effective compared with triptorelin.	4.19 4.21
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable.	
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 Implementation

Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires

clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.1 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has advanced hormone-dependent prostate cancer and the doctor responsible for their care thinks that degarelix is the right treatment, it should be available for use, in line with NICE's recommendations.

5.2 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Proposed recommendations for further research

6.1 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 metastases and people with impending ureteric and urethral obstruction. Research should be planned as part of well-conducted randomised clinical trials.

7 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 clinical guideline 175 (2014).
- Metastatic spinal cord compression: diagnosis and management of adults at risk of and with metastatic spinal cord compression. NICE clinical guideline 75 (2008).
- Improving outcomes in urological cancers. Cancer service guidance (2002).

8 Review of guidance

8.1 The guidance on this technology will be considered for review in May 2017. 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
April 2014

9 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 Lindsay Smith (Vice Chair)
General Practitioner, West Coker Surgery, Somerset

Dr Graham Ash

Consultant in General Adult Psychiatry, Lancashire Care NHS Foundation Trust

Dr Andrew Black
General Practitioner, Mortimer Medical Practice, Herefordshire

Professor David Bowen
Consultant Haematologist, Leeds Teaching Hospitals NHS Trust

Dr Ian Campbell
Honorary Consultant Physician, Llandough Hospital, Cardiff

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

Susan Dutton
Senior Medical Statistician, Oxford Clinical Trials Research Unit

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

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 & 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 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

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
Technical Adviser

Kate Moore
Project Manager

10 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 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. Manufacturer/sponsor:

- Ferring Pharmaceuticals

II. Professional/specialist and patient/carer groups:

- Prostate Cancer Support Federation
- Prostate Cancer UK
- 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):

- Commissioning Support Appraisals Service
- 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 specialist and patient expert nominations from the consultees and commentators. They gave their expert personal view on degarelix by attending the initial Committee discussion 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 specialist
- Dr Isabel Syndikus, Consultant Clinical Oncologist, nominated by the Royal College of Physicians – clinical specialist
- David Baxter-Smith, nominated by Prostate Cancer Support Federation – patient expert
- Stuart Watson, nominated by Prostate Cancer UK – patient expert

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

- Ferring Pharmaceuticals