NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Degarelix for treating advanced hormone-dependent prostate cancer

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- The manufacturer's submission presented clinical effectiveness data from 6 randomised controlled trials (RCTs) that compared degarelix with luteinising hormone-releasing hormone (LHRH) agonists (alone or in combination with short-term anti-androgen flare treatment with bicalutamide). The Evidence Review Group (ERG) noted that these trials included patients with all stages prostate cancer (localised, not classifiable, locally-advanced and metastatic) and that prostate specific antigen (PSA) levels and the proportion of patients who received bicalutamide were lower than what would be expected in UK clinical practice. The ERG also noted that the proportion of patients who received treatment with anti-androgen therapy for flare protection in the main trial was also lower than what would be expected in UK clinical practice. What is the Committee's view on the generalizability of the trial results to UK clinical practice?
- The manufacturer conducted simple pooled analyses rather than meta-analyses from the RCTs of degarelix for the outcomes: testosterone response and PSA response. The ERG considered that the method of pooling used was not

appropriate and the manufacturer's results should be interpreted with caution. What is the Committee's view on the pooled results presented by the manufacturer?

- The manufacturer presented data from the main clinical trial, CS21, in terms of PSA response comparing the licensed dose of degarelix (240/80 mg), an unlicensed dose of degarelix (240/160 mg) and leuprorelin 7.5 mg. The estimated probabilities of completing the study without PSA progression were 91.1% (95% CI 85.9% to 94.5%) for patients receiving degarelix 240/80 mg, 85.8% (95% CI 79.8% to 90.1%) for patients receiving degarelix 240/160 mg, and 85.9% (95% CI 79.9% to 90.2%) for patients receiving leuprorelin 7.5 mg. What is the Committee's view on the PSA response results presented by the manufacturer for the different doses of degarelix?
- The manufacturer conducted meta-analyses from the RCTs of degarelix. The ERG noted that the CS35 had been included inappropriately and that the results for overall survival should be interpreted with caution because the study duration of the included trials was too short and they were not designed to detect differences in survival. What is the Committee's view on the results of the manufacturer's meta-analyses?
- The manufacturer carried out a mixed-treatment comparison (MTC) to demonstrate similar efficacy between LHRH agonists and the relative efficacy of degarelix compared with bicalutamide. Overall survival was the only outcome included in the MTC. Although no statistically significant differences were found, additional analyses conducted by the ERG seemed to indicate that mortality for triptorelin was lower than for leuprorelin. The ERG also expressed concern that it may not be appropriate to compare these treatments solely on the basis of this outcome because the time horizon of the studies was short and none were powered to detect difference in survival in this population. What is the Committee's view on the results of the manufacturer's MTC?
- The manufacturer presented results of adverse events, including the risk of fractures, joint-related symptoms, urinary tract events and cardiovascular events, based on pooled analyses of individual patient data from the RCTs evaluated post-hoc. The ERG considered that meta-analyses should have been conducted instead of simple pooled analyses and that these results should be treated with

caution. What is the Committee's view on the adverse events results presented by the manufacturer?

- The manufacturer's submission excluded bicalutamide monotherapy on the basis that it is only indicated for patients with locally advanced disease, and there was lack of trial data directly comparing degarelix with bicalutamide monotherapy. The ERG believed that it may have been possible to conduct naïve indirect comparisons of bicalutamide monotherapy versus degarelix for selected outcomes using data for the locally advanced subgroups within the degarelix trials. Does the Committee consider the exclusion of bicalutamide monotherapy from the indirect comparison to be appropriate?

Cost-effectiveness

- The ERG noted that the assumption of equivalent efficacy and adverse events between LHRH agonists used in the manufacturer's economic model was not adequately justified and that it would have been more appropriate to model the treatment effect of each LHRH agonist individually. It also suggested that it was more appropriate to use all RCT data and to assume a relative benefit from degarelix compared with LHRH agonists only for the trial duration (1 year). What is the Committee's view on the manufacturer's assumption that LHRH agonists are equivalent in efficacy and adverse events and the ERG's additional analyses which assume differential efficacy between treatment arms only for 1 year?
- The manufacturer assumed that there was a relationship between PSA progression and overall survival and applied an increased risk of mortality to the model for those patients with metastatic disease. The ERG considered the data supporting the relationship to be inconclusive. What is the Committee's view on the plausibility of the manufacturer's assumption that there is a relationship between PSA progression and overall survival?
- The treatment sequence presented in the manufacturer's model was based on NICE clinical guideline 58, European Association of Urology (EAU) guidelines and advice from clinical specialists. It assumed that treatment with degarelix or LHRH agonists stopped when the disease became hormone-refractory. This treatment pathway was mirrored in the manufacturer's economic model. The ERG presented an alternative treatment sequence in which treatment with degarelix or LHRH

agonists was continued until death and the proportion of patients receiving chemotherapy after PSA progression was assumed to be 70% and the proportion of patients receiving abiraterone was assumed to be 70%. What is the Committee's view on the plausibility of these assumptions?

- The manufacturer applied a mapping algorithm from Kontodimopoulos et al (2009) to transform the health-related quality of life data from CS21 into EQ-5D utility values and used these results in its economic analysis. What is the Committee's view on the utility values used in the manufacturer's model?
- The manufacturer's base-case results showed that degarelix dominated LHRH agonists (that is, degarelix was less costly and more effective).The ERG considered that a most plausible scenario included triptorelin as the most appropriate comparator, it assumed that treatment with degarelix or triptorelin was continued until death, it only assumed a relative benefit from degarelix during the first year and varied the proportion of patients who would receive chemotherapy and abiraterone in the economic model. The ERG's base-case results showed an incremental cost-effectiveness ratio of £14,798 per QALY gained for degarelix compared with triptorelin. What is the Committee's view on the most plausible ICER for degarelix?
- The manufacturer presented subgroup analyses for those patients at high risk of disease progression (PSA levels at baseline greater than 20ng/ml) and for those patients with cardiovascular disease at baseline. The results for the high risk population were similar to those for the intention to treat population. The results for those patients with cardiovascular disease at baseline showed an incremental cost-effectiveness ratio (ICER) of £4216 per QALY gained for degarelix compared with goserelin. What is the Committee's view on the results of the subgroup analyses presented by the manufacturer?
- The results from the manufacturer's model were most sensitive to the hazard ratio for PSA progression and the parameters that had the highest impact on the ICER were the efficacy and safety profile of degarelix. The ERG considered, based on its additional analyses, that the parameters that had the highest impact on the ICER were: the exclusion of spinal cord compression (SCC) adverse events from the analysis; the modelling of the rates of fractures; the assumption that PSA progression affected mortality rates in metastatic patients; and the assumption of

equal efficacy of degarelix and LHRH agonists. What is the Committee's view on the key drivers of the cost-effectiveness results for degarelix?

- The ERG carried out a subgroup analysis for patients with spinal metastasis with actual or impending SCC. It concluded that degarelix dominated triptorelin. What is the Committee's view on the results of this analysis?

1 Background: clinical need and practice

1.1 Prostate cancer is a disease in which tumours develop in the prostate, a gland in the male reproductive system. Its cause is thought to involve both environmental and genetic factors. Locally advanced prostate cancer encompasses a spectrum of disease states, including extension of the disease through the prostate capsule, spread to affect the seminal vesicles, and spread to adjacent structures including the bladder neck, external sphincter, rectum, levator muscles and pelvic wall. The condition may also be described as locally advanced when it has spread to affect the regional lymph nodes. Eventually, metastases may develop distant from the prostate gland, when the disease is described as metastatic.

1.2 In 2010, there were approximately 41,000 men newly diagnosed with prostate cancer and over 10,700 deaths from prostate cancer in the UK. It is the second most common cause of death in men with any cancer in the UK. In England, over 81% of the people with prostate cancer survive 5 years or more. The incidence of prostate cancer increases with age and is higher in men of African-Caribbean family origin. As prostate cancer is more common in older populations, it affects those in whom cardiovascular-related disease and osteoporosis and related fractures are also more common.

1.3 NICE clinical guideline 58 on prostate cancer recommends that people with localised disease should be offered active surveillance, prostatectomy (surgical removal of the prostate) or high-dose radical radiotherapy. Long-term disease-free intervals are commonly associated with surgical or radiotherapeutic treatment in more than 60% of people

with localised disease but this is uncommon in people with advanced prostate cancer. Advanced prostate cancer is defined as locally advanced or metastatic disease (that is, where the cancer has spread beyond the prostatic capsule). Around 55–65% of people with prostate cancer develop metastatic disease. NICE clinical guideline 58 recommends hormonal therapy for people with locally advanced prostate cancer who are receiving radical radiotherapy. Treatment with gonadotrophin-releasing hormone agonist therapy (GnRH) (also known as luteinising hormone-releasing hormone [LHRH] agonists) is recommended before and during radical radiotherapy. Hormonal therapy is additionally recommended after radical radiotherapy for those with a Gleason score of 8 or more (which indicates a poorer prognosis). NICE clinical guideline 58 also recommends hormonal therapy for people with prostate cancer who experience a biochemical relapse after radical (prostatectomy or radiotherapy) treatment if they have symptomatic local disease progression, metastases or a prostate-specific antigen doubling time of less than 3 months. Standard hormonal treatments for metastatic disease include use of a LHRH agonist, such as goserelin, leuprorelin or triptorelin, or bilateral orchidectomy (surgical removal of the testes). Bicalutamide monotherapy (150 mg) is a treatment option for people with metastatic prostate cancer who are willing to accept the adverse impact on overall survival and gynaecomastia (enlargement of breast tissue) in the hope of retaining sexual function. NICE clinical guideline 58 notes that bicalutamide does not have UK marketing authorisation for this indication and informed consent should be obtained and documented. During the first weeks of LHRH agonist therapy, an initial and temporary rise in serum testosterone (flare-up) can occur, which may be managed using anti-androgens. The clinical impact of flare-up is unknown, except in patients with impending spinal cord compression (SCC) for whom other strategies for immediately ablating testosterone levels, such as bilateral orchidectomy, should be considered.

2 The technology

2.1 Degarelix (Firmagon, Ferring Pharmaceuticals) is a selective gonadotrophin releasing hormone (GnRH) antagonist that reduces the release of gonadotrophins by the pituitary, which in turn reduces the secretion of testosterone by the testes. Because they do not produce a rise in hormone levels at the start of treatment, GnRH antagonists do not initially induce testosterone surge or tumour stimulation, or have the potential for symptomatic flare. Degarelix has a UK marketing authorisation for 'treatment of adult male patients with advanced hormone-dependent prostate cancer'. It is administered as a subcutaneous injection.

2.2 The licensed dose of degarelix is an initial loading dose of 240 mg administered as 2 subcutaneous injections of 120 mg each, followed by a monthly maintenance dose of 80 mg administered as 1 subcutaneous injection.

2.3 The summary of product characteristics lists the following adverse reactions for degarelix: hot flushes, weight increase and injection site adverse events (such as pain and erythema). For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.4 The list price of degarelix is £260.00 for the starting dose of 2 120-mg vials and £129.37 per 80-mg vial for each monthly maintenance dose (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's estimate of the average duration of treatment with degarelix was 5.4 years and the total time spent on treatment was 5.9 years (including time spent receiving combined androgen blockade and anti-androgen withdrawal). Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of degarelix within its licensed indication for treating advanced hormone-dependent prostate cancer.

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Adults with advanced hormone-dependent prostate cancer (locally advanced or metastatic, including biochemical relapse) in whom orchidectomy is not preferred	

The ERG noted that the population described in the manufacturer's submission was in line with the final scope issued by NICE. However, the ERG commented that a substantial proportion of patients with localised and non-classifiable prostate cancer were included in the 6 RCTs presented by the manufacturer. The ERG received expert advice suggesting that inclusion of patients with these types of prostate cancer resulted in lower median baseline levels of prostate specific antigen (PSA) than what would be expected in UK clinical practice for those patients receiving hormonal therapy.

	Final scope issued by NICE	Decision problem addressed in the submission
Intervention	Degarelix	

The ERG noted that the manufacturer's description of the intervention was in line with the marketing authorisation for degarelix.

	Final scope issued by NICE	Decision problem addressed in the submission
Comparators	• Gonadotrophin-releasing hormone agonists in combination with short-term anti-androgen treatment including: ○ Goserelin ○ Leuprorelin ○ Triptorelin • Bicalutamide	• Gonadotrophin-releasing hormone agonists in combination with short-term anti-androgen treatment including: ○ Goserelin ○ Leuprorelin ○ Triptorelin

The manufacturer's submission included the LHRH agonists goserelin, leuprorelin, and triptorelin in combination with short-term anti-androgen treatment which is consistent with the final scope. The manufacturer stated that goserelin was selected as the comparator for the base case economic analysis, with the other LHRH agonists being compared in scenario analyses. The manufacturer's clinical Advisory board recommended this approach based on volume of sales data in England and Wales during 2011-12 which showed that goserelin is the most commonly used LHRH agonist in the UK for treating prostate cancer. The ERG noted that the main clinical trial that informed the economic model compared degarelix with leuprorelin.

The manufacturer's submission stated that bicalutamide monotherapy was not included as a comparator due to the lack of comparative evidence with degarelix and/or LHRH agonists. The manufacturer stated that it was not possible to conduct a robust mixed treatment comparison (MTC). Furthermore, the manufacturer stated that the licensed indications for bicalutamide monotherapy and degarelix are not equivalent because bicalutamide monotherapy (150 mg) is only licensed for use in people with locally advanced non-metastatic prostate cancer; therefore it is only of relevance to a subset of the population.

The ERG commented that bicalutamide monotherapy represents a treatment option for a proportion of patients, particularly those with locally advanced disease and for younger patients in whom maintenance of sexual function is preferable. The ERG noted that a naïve indirect comparison of degarelix with bicalutamide monotherapy may have been possible for selected outcomes using data for the locally advanced subgroups within the 6 degarelix RCTs.

	Final scope issued by NICE	Decision problem addressed in the submission
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rate • Testosterone response • Prostate-specific antigen (PSA) response • Time to PSA progression • PSA progression-free survival • Adverse effects of treatment • Health-related quality of life.	

The ERG noted that the outcome measures included in the manufacturer's submission were consistent with the final scope.

	Final scope issued by NICE	Decision problem addressed in the submission
Economic evaluation	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	

The manufacturer expressed cost effectiveness estimates as the incremental cost per quality-adjusted life year (QALY). The time horizon used in the model was 30 years, and costs were considered from the NHS and Personal Social Services perspective.

	Final scope issued by NICE	Decision problem addressed in the submission
Subgroups	• High-risk patients with PSA >20 ng/ml • Patients with spinal metastases with impending or actual spinal cord compression • Patients with high tumour volume with impending or actual urinary outflow obstruction • Patients with bony metastases associated with intractable pain • Patients for whom standard anti-androgen treatment is contraindicated • Patients at risk of evolving cardiovascular comorbidity.	• High-risk patients with PSA >20 ng/ml • Patients with pre-existing cardiovascular disease

The manufacturer's submission included 2 of the subgroup analyses specified in the NICE scope: patients with PSA levels of greater than 20ng/ml using efficacy data from the CS21 RCT, and patients with pre-existing cardiovascular disease (that is, patients with a history of myocardial infarction, ischaemic cerebrovascular conditions, haemorrhagic cerebrovascular conditions, embolic and thrombotic events arterial, and other ischemic disease) using a post-hoc pooled analysis from the 6 RCTs of degarelix. The manufacturer stated that there was insufficient evidence in the RCTs to carry out a robust cost effectiveness analysis for the other subgroups in the final scope. The ERG noted that while there is a correlation between LHRH antagonists and anti-androgen therapy and cardiovascular mortality, there is currently a lack of prospectively designed trials which could adequately examine this relationship.

3.2 In this appraisal, the manufacturer has positioned degarelix as an alternative to LHRH agonists and made the assumption that when the disease becomes refractory to first-line hormonal therapy, patients receive treatment with chemotherapy (docetaxel) and abiraterone thereafter. For further information please see section 6.21.

4 Clinical-effectiveness evidence

4.1 The manufacturer conducted 2 systematic reviews, 1 to identify clinical evidence for degarelix in the target population of adult men with advanced hormone-dependent prostate cancer (locally advanced or metastatic, including biochemical relapse) in whom orchidectomy was not preferred, and a second to identify clinical evidence for the comparators to inform a mixed treatment comparison.

4.2 The manufacturer identified 6 randomised controlled trials (RCT) that compared degarelix with LHRH agonists, 5 randomised dose-finding trials of degarelix and 7 non-randomised studies that were relevant to the decision problem. The 6 RCTs were supplemented by the manufacturer's clinical study reports.

4.3 Of the 6 RCTs included in the manufacturer's submission, the main clinical trial (CS21 [n=610]) compared degarelix with leuprorelin with or without concomitant bicalutamide, 4 trials compared degarelix with goserelin with or without concomitant bicalutamide (CS28 [n=42], CS30 [n=246], CS31 [n=182] and 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 RCTs were open label, conducted in the USA and/or Europe and were primarily designed to demonstrate that degarelix was non-inferior to LHRH agonists for treating prostate cancer. The manufacturer noted that blinding of patients and care providers was not possible because of different formulations and methods of administration of degarelix and LHRH agonists and stated that although this may not have introduced any bias in objectively measured outcomes, it could have had an impact in the assessment of subjectively measured outcomes (such us adverse events, international prostate symptom score [IPSS] and quality of life). In CS21 the treatment was blinded to the central laboratory personnel. Table 1 shows a summary of the intervention and comparator groups in the included RCTs.

Table 1: Summary of the intervention and comparator groups in the included RCTs

Trial	Intervention	Randomised	Comparator	N randomised	Duration
CS21 Klotz et al, 2008	Degarelix 240mg Monthly 80mg or Degarelix Initial 240mg Monthly 160 mg	n=210 n=206	Leuprorelin 7.5mg Monthly 7.5mg (with or without bicalutamide flare protection)	n=204 23/201 (11%) received flare protection	12 months
CS28 Anderson et al., 2013	Degarelix 240mg Monthly 80mg	n=29	Goserelin 3.6mg on days 3, 31, and 59 and bicalutamide on days 0-17	n=13 All reported to receive flare protection	3 months
CS30 Mason et al., 2013	Degarelix 240mg Monthly 80mg	n=181	Goserelin 3.6mg on days 3, 31, and 59 + bicalutamide 50mg daily on days 0-16	n=65 All reported to receive flare protection	3 months
CS31 Axcrona etal., 2012	Degarelix 240mg Monthly 80mg	n=84	Goserelin 3.6mg on day 0, 28, and 56 + bicalutamide 50mg daily on days 0-28	n=98 All reported to receive flare protection	3 months
CS35	Degarelix 240mg 3-monthly 480mg	n=572	Goserelin 3.6mg 3-monthly 10.8mg, with or without bicalutamide for up to 28 days	n=287 38 (13.5%) received flare protection	13 months
CS37	Degarelix intermittent 240mg 6 maintenance doses of 80 mg at days 28 to 168 Degarelix continuous 240mg 13 maintenance doses of 80 mg at days 28 to 364	n=177 n=50	Leuprorelin 7.5mg 3-monthly 22.5mg	n=182 Flare protection not reported	14 months

Source: ERG's report, table 4, page 25

4.4 All RCTs included adult patients with histologically confirmed prostate cancer in whom endocrine treatment was indicated. Prostate specific antigen (PSA) level was an eligibility criterion in all 6 RCTs with baseline PSA levels of 2ng/ml or more in CS21, CS31 and CS35 and of 10ng/ml or more in CS28 and CS30. In CS37, patients had to have rising PSA levels

after having undergone primary therapy for localised prostatic carcinoma (either a rise in PSA levels of 0.2ng/ml or more after radical prostatectomy or 3 PSA levels higher than the lowest PSA level observed after radiation, cryotherapy or LHRH agonists' treatment) and the investigator assessed that androgen deprivation therapy was warranted. In CS35, PSA levels in patients whose disease recurred after radical prostatectomy should have shown an increase of 0.2ng/ml or more from the previous test on 2 consecutive measurements. An ECOG score of 2 or less was an eligibility criterion in CS21, CS28, CS30, CS35 and CS37.

4.5 The manufacturer stated that there were no statistically significant differences in the main baseline characteristics between treatment groups within each RCT although p values were not reported. Age and testosterone levels were comparable across the trials, while a range of PSA values were seen both within and between trials. The proportion of patients with either locally advanced or metastatic prostate cancer ranged from 5.5% in CS37 to 60% in CS31.

4.6 The main outcome measures included in each trial are summarised in table 2. The primary endpoints in the trials were defined as suppression of serum testosterone levels to 0.5ng/ml or less (castrate levels) between day 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 at 12 weeks in CS28 and PSA suppression (PSA levels of 4ng/ml or less) at 14 months in CS37. The manufacturer stated that PSA progression, defined as 2 increases of more than 50% above baseline, is used routinely in clinical practice as a prognostic indicator to assess disease progression and/or treatment response.

Table 2 Summary of the main outcome measures of the included RCTs

Main outcomes	CS21	CS28	CS30	CS31	CS35	CS37
Overall survival	x	x	x	x	x	x
Progression-free survival	x				x	x
Testosterone response [a]	x (primary)	x	x	x	x (primary)	x
PSA response	x	x	x	x	x	x

						(primary)
Prostate volume (size)		x	x (primary)	x (primary)		
IPSS		x (primary)	x	x	x	
Health-related QoL	x	x	x	x	x	x
Adverse effects	x	x	x	x	x	x

Key: IPSS = International Prostate Symptom Score; PSA = prostate-specific antigen; QoL = quality of life
[a] Serum testosterone levels
Source: ERG's report, table 11, page 43

4.7 The manufacturer's submission presented the results of the 6 RCTs in a narrative synthesis. The manufacturer also presented pooled analyses and meta-analyses using data from different combinations of the 6 RCTs. It also presented a mixed treatment comparison (MTC) using data from the RCTs and additional studies; but it should be noted the results of this analysis were not incorporated into the manufacturer's economic model. Table 3 summaries the outcomes and analyses in the manufacturer's submission.

Table 3 Summary of outcomes and analyses in the manufacturer's submission

Outcomes reported in of MS	Narrative from individual trials	Pooled analyses from trials	Meta-analysis from trials	MTC with published studies of comparators
Overall survival	x		x	x
Progression free survival [a]	x			
Testosterone response [b]	x	x		
PSA response	x	x[e]	x	
Time to PSA progression				
PSA progression-free survival [d]	x	x[f]		
Adverse events of treatment		x	x	
Health-related quality of life	x			
Prostate volume [c]	x		x	
International prostate symptom score (IPSS)	x		x	
Serum alkaline phosphatase (s-ALP)	x	x		

[a] Raw data not presented in the MS
[b] Serum testosterone levels in the MS (page 52). Page 65 defines testosterone response as "cumulative probability of testosterone levels ≤0.5 ng/ml from Day 28 to 84)".
[c] Described as 'prostate size reduction' in the MS
[d] PSA progression (recurrence/failure) defined as two consecutive increases of 50% and ≥5 ng/ml compared to nadir in CS21 (page 67 of the MS)
[e] Analysis mentioned but data not provided
[f] Using pooled data from those who received anti-flare protection (69/414) LHRH versus 974 degarelix from total sample of 1,457
Source: ERG's report, table 2, page 19

4.8 The results from the analysis of the primary endpoint, testosterone response, from the main trial (CS21) and CS35 are summarised in table 4. The manufacturer stated that degarelix showed a rapid suppression of testosterone levels that indicated a rapid onset of action and, as a result, the possibility of rapid disease control. The manufacturer also estimated the cumulative probability of achieving testosterone levels of 0.5ng/ml or less from day 28 to 364 in the ITT population and concluded that degarelix (including only the licensed dose of 240/80mg) showed non-inferiority compared with leuprorelin (non-inferiority limit of -10 percentage points).

Table 4 Testosterone response in CS21 and CS35

Outcome reported	Degarelix	Comparator	Statistical difference
Cumulative probability testosterone levels (95% CI) ≤0.5 from Day 28 to Day 364 in CS21	97.2% (93.5% to 98.8%) 240/80 mg 98.3% (94.8% to 99.4%) 240/160 mg	96.4% (92.5% to 98.2%) leuprorelin 7.5 mg group	Difference 0.9% 95% CI 3.2% to 5% Kaplan Meier 97.5% two-sided (multiplicity-adjusted) CI greater than non-inferiority to leuprorelin 7.5 mg limit of –10 % points
Testosterone flare on days 1, 3, 7 and 14 in CS21*	n=0 (0%) 240/80 mg arm n=1 (0.2%) 240/160 mg arm	n=161 (80.1%) leuprorelin 7.5 mg group	(p<0.0001, Fisher's exact test)
Testosterone levels ≤0.5 ng/ml on day 3 in CS21	199 (96.1%) 240/80 mg arm	n=0 (0%) leuprorelin 7.5 mg group	p<0.0001
Cumulative probability (95% CI) of testosterone levels ≤0.5 ng/ml from Day 3 to Day 364 in CS35**	85.0% (81.6% to 87.8%)	5.3% (3.1% to 8.4%) for goserelin	NR
Cumulative probability of testosterone levels ≤0.5 ng/ml from Day 28 to Day 364 in CS35	90.0% for degarelix	96.7% for goserelin	NR

*It should be noted that only in the comparator arm 11% had bicalutamide flare protection as would be administered in UK clinical practice.
** It should be noted that only 13.5% of patients in the goserelin group received anti-androgen protection against a testosterone flare (surge) at the start of the treatment.
Key: CI: Confidence interval
Source: ERG's report, table 12, page 45

4.9 The manufacturer combined the estimated cumulative probabilities of achieving testosterone levels of 0.5ng/ml or less from 4 RCTs (CS21,

CS28, CS30 and CS31), and the results are presented in table 5. The manufacturer stated that the results from these RCTs were consistent with the findings from CS21, indicating that a monthly maintenance regimen of degarelix is at least as effective as LHRH agonist therapy in reducing serum testosterone levels.

Table 5 Cumulative probability of testosterone levels ≤0.5ng/ml combining data from CS21, CS28, CS30 and CS31

Intervention	Estimate (95% CI)
Day 28–84	
Degarelix	98.0% (96.2% to 98.9%)
LHRH agonists	96.2% (93.7% to 97. 7%)
Day 28–364	
Degarelix	95.7% (92.4% to 97.6%)
LHRH agonists	94.7% (91.4% to 96.7%)

Key: CI = confidence interval; LHRH = luteinising hormone-releasing hormone

Source: manufacturer's submission, table 15, page 74

4.10 In the main trial (CS21) PSA progression was defined as having 2 consecutive increases in PSA level of 50% or more and of more than 5ng/ml compared with the lowest level observed. The probability of completing the study without PSA progression on day 364 using the Kaplan-Meier method was 91.1% (95% CI 85.9% to 94.5%) in patients receiving the licensed dose of degarelix (240/80 mg), 85.8% (95% CI 79.8% to 90.1%) in patients receiving the unlicensed dose of degarelix (240/160 mg) and 85.9% (95% CI 79.9% to 90.2%) in patients receiving leuprorelin. The manufacturer also presented data on the median percentage changes in PSA levels from baseline to different time points from CS21, CS28, CS30, CS31 and CS35. The manufacturer stated that the difference in the median change in PSA levels between degarelix and leuprorelin in CS21 was statistically significant on days 14 and 28 ($p<0.0001$) indicating that degarelix showed more rapid PSA control than leuprorelin (see table 6).

Table 6 Median percentage change in PSA levels across individual trials

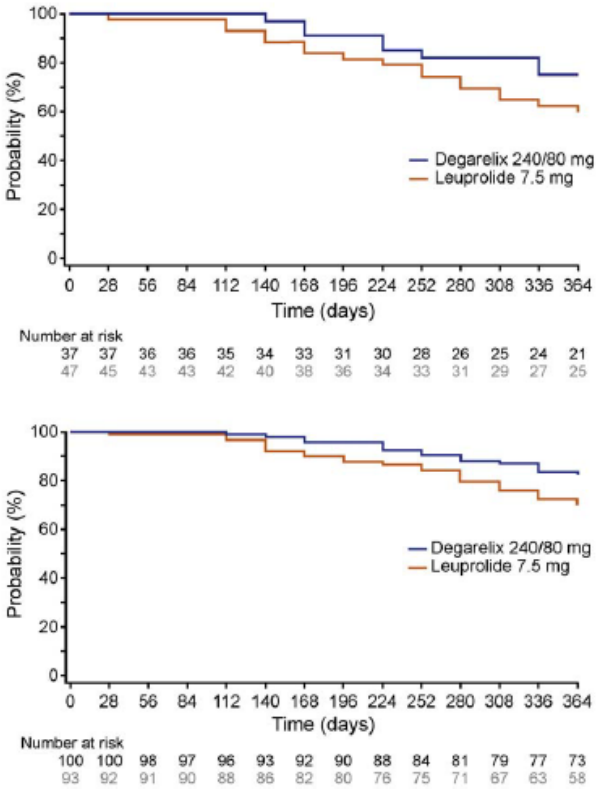
Outcome reported	Degarelix	Comparator	Statistical difference
Baseline to day 14 in CS21	–63.4% (IR–77.1% to –48.4%)	–17.9% (IR–35.5% to –5.2%) in the leuprorelin group	p<0.0001, (Wilcoxon test)
At Day 28 in CS21	–84.9% (IR- 91.6% to –73.2%) 240/80 mg arm	–17.9% (IR –35.5% to –5.2%)	p<0.0001, (Wilcoxon test)
Baseline to Week 8 in CS28	–89.2% (min–max range –99.5% to –31.6%)	–97.3% (–99.7% to –87.6%) for goserelin plus bicalutamide	NR
At Week 4 in CS30	–71.6% (min–max range –98.3% to 64.3%)	–72.2% (–97.0% to 65.5%) for goserelin plus bicalutamide	NR
At Week 12 in CS30	89.2% (–99.8% to –37.2%	93.0% (–98.9% to –54.6%)	NR
Baseline to Week 4 in CS31	–80.6% (min–max range –99.1% to 45.5%)	–85.2% (–99.8% to 47.8%)	NR
At Day 28 in CS35	–84% (interquartile range –92% to –71%)	–66% (–83 to –49%) for goserelin	p<0.0001
At day 84 & day 364 in CS35	94% 96%	94% 98%	NR

Note: Only the results for the licensed dose of degarelix (240/80 mg) from the CS21 are presented here.
Source: ERG's report, table 15, page 47

4.11 The manufacturer also conducted 2 post hoc exploratory subgroup analyses on PSA progression: PSA progression depending on the stage of the disease and PSA progression for those patients with PSA level at baseline of more than 20ng/ml. In the first analysis, results showed that PSA progression occurred more frequently in patients with advanced disease and results from the second analysis showed that PSA progression occurred more frequently in patients with a PSA level at baseline of more than 20ng/ml (see figure 1). There was no statistically significant difference between treatment arms in the proportion of patients with metastatic disease who experienced PSA progression (21.6% and 36.2% in the degarelix and leuprorelin groups respectively, p=0.156) and this proportion was also similar in patients with locally advanced disease (10.9% and 11.5% in the degarelix and leuprorelin groups respectively, p value not reported). The difference between treatment arms in the proportion of patients who had PSA progression was statistically significant in patients with baseline PSA level of 20ng/ml or more (16.0%

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

Figure 1 Probability of being free of PSA recurrence in patients with baseline metastatic disease (top) or baseline PSA level of more than 20ng/ml (bottom)



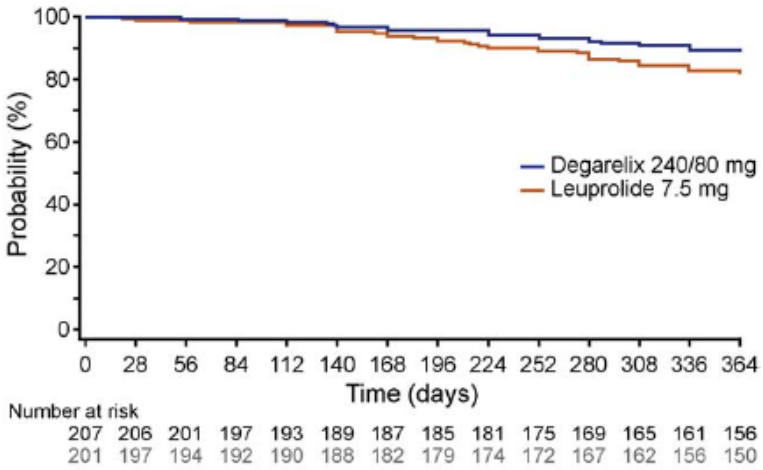
Source: Manufacturer's submission, appendix b, figure b1

4.12 Results from the main trial (CS21) were pooled with data from the CS35 trial (n=1475) to compare patients in the degarelix group (n=974) and those patients who received LHRH agonists plus anti-androgen treatment (n=69). It was assumed that there were no differences between individual studies. The manufacturer stated that the PSA PFS failure rate (adjusted for baseline PSA levels, stage of prostate cancer and Gleason score) was statistically significantly lower with degarelix compared with LHRH agonists plus anti-androgen treatment (HR 0.490, p=0.0028). For those patients who had PSA levels of more than 20ng/ml this difference was also statistically significant between treatment groups (HR 0.500, p=0.0073). The manufacturer also mentioned that this pooled analysis showed a more rapid PSA suppression with degarelix compared with

LHRH agonists plus anti-androgen treatment and that in patients with metastatic disease, mean percentage PSA reduction was greater in patients receiving degarelix compared with patients in the LHRH agonists plus anti-androgen group. The manufacturer did not provide any data relating to these statements.

4.13 The manufacturer presented an analysis of the risk of PSA progression or death from the CS21 trial. These results showed that patients receiving degarelix had a lower risk of PSA progression or death compared with patients receiving leuprorelin (p=0.05) (see figure 2). The manufacturer also reported results on 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 differences between treatment groups in terms of disease progression in CS37 or CS35.

Figure 2 Probability of PSA progression or death in CS21

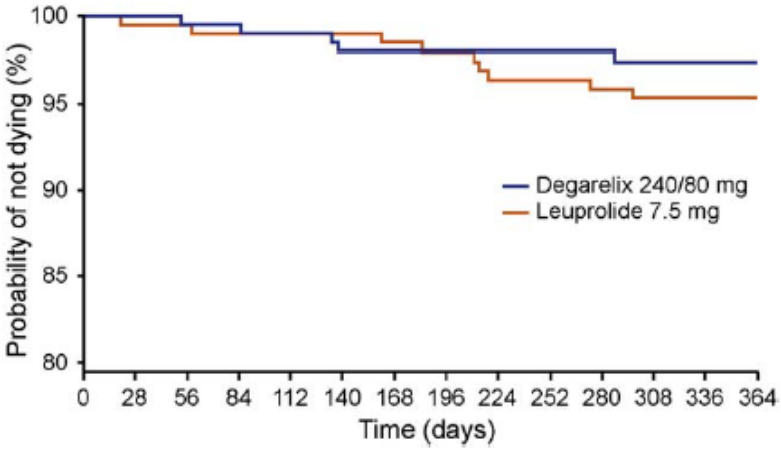


Source: Manufacturer's submission, appendix B, figure B3

4.14 The results for overall survival from the CS21 trial showed that 5 patients (2% of 207) and 9 patients (4% of 201) died in the degarelix and leuprorelin arms respectively. The risk of death was 2.6% (95% CI 1.1% to 6.2%) for patients receiving degarelix and 4.9% (95% CI 1.1% to 6.2%) for patients receiving leuprorelin arm (see figure 3). 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 that because of the short follow-up, the number of deaths were low.

Figure 3 Probability of death in CS21



Source: Manufacturer's submission, appendix B, figure B2

4.15 The manufacturer presented results of the IPSS questionnaire from CS28, CS30, CS31 and CS35. It noted that the IPSS questionnaire is used to assess the severity of urinary obstruction with lower urinary tract symptoms (LUTS). A reduction in the IPSS indicates improvement in LUTS. The results from all the trials showed a greater reduction in the IPSS in the degarelix groups compared with the LHRH agonists group. The manufacturer also reported results on prostate volume, noting that a reduction in the size of the prostate gland is a mechanism to achieve a relief in LUTS. The manufacturer stated that the results from CS28, CS30 and CS31 trials indicated that degarelix was non-inferior to LHRH agonists in reducing the prostate size.

4.16 The manufacturer presented data for health-related quality of life assessed with different measures and questionnaires in each of the 6 RCTs. In CS21, quality of life was evaluated using the short form 12 version 2 (SF12 v2) and the European Organization for Research and treatment of cancer, quality of life – C 30 (EORTC QLC-C30)

questionnaires to obtain generic and cancer-specific measures of quality of life respectively. The manufacturer used a single question of the IPSS questionnaire related to urological symptoms to measure quality of life in CS28, CS30 and CS31. In CS31, quality of life was also addressed using the benign prostatic hyperplasia impact index (BPHII), which measures how urinary problems affect various domains of health. The SF-36 v2 instrument and the visual analogue scale (VAS) were used in CS35 to measure generic quality of life and pain respectively. In CS37, the manufacturer used the functional assessment of cancer therapy – prostate (FACT-P) instrument to assess quality of life and the sexual function index (SFI) to assess sexual function. The results are outlined in table 7.

Table 7 Summary of health-related quality of life results from the individual trials

Outcome reported	Degarelix	Comparator	Statistical difference
CS21 SF-12 v2 & EORTC QLQC30	no changes from baseline scores in any of the eight SF-12 domains assessed were observed		
CS28 supplementary question about urinary symptoms in the IPSS (mean decreases from baseline indicate improvement)	Week 4: 0.96 Week 8: 1.54 Week 12: 1.77	Week 4: 0.54 Week 8: 0.73 Week 12: 0.55	NR
CS30	no overall significant differences in the change in quality of life scores from baseline to Week 4, 8 or 12 were seen between treatment groups		
CS31 proportion of patients who felt delighted, pleased or mostly satisfied with their urinary condition increased from baseline to Week 12	38% to 72%	48% to 76% in the goserelin plus bicalutamide group	NR
CS31 mean reduction in the BPHII score at Week 12	–1.28	–1.16	NR
CS35, all SF-36 scores	comparable across treatment groups and trial days, and no changes from baseline scores occurred during the trial in any of the eight domains.		
CS35 change in VAS from baseline in metastatic prostate cancer	a greater decrease with degarelix than with goserelin was observed at Day 28		p=0.0438
CS37 FACT-P survey	no statistically significant difference was observed over a range of visits or through to the end of the study for any domains.		
CS37 SFI inventory	Apparent relationship between return to testosterone levels >0.5ng/ml and improved SFI scores in those patients receiving intermittent degarelix.		

Source: adapted from ERG's report, table 21, page 62

4.17 As described in table 3, the manufacturer included the following outcomes in the meta-analyses: testosterone response, prostate size reduction, IPSS, PSA response and overall survival. For the cumulative probability of testosterone levels of 0.5ng/ml or less, it pooled the data from 4 RCTs (CS21, CS28, CS30 and CS31), and the analysis updated during clarification also included data from CS35. The manufacturer noted that there was statistically significant heterogeneity between trials. For the differences in the percentage change in PSA levels the manufacturer included data from CS21, CS28, CS30, CS31 and CS35. The results showed that there was statistically significant heterogeneity between trials. The manufacturer suggested that this heterogeneity across trials for the PSA response could be due to different baseline PSA levels according to different eligibility criteria in the trials. For the percentage change in prostate volume, the manufacturer included data from the CS28, CS30 and CS31 trials. 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 changes in IPSS, the manufacturer included data from CS28, CS30 and CS31 and the mean differences in changes in IPSS between degarelix and LHRH agonists when pooling the results 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 in terms of odds ratio (OR) pooling data from the CS21, CS28, CS30, CS31 and CS35 trials. The results showed that the mortality risk was lower in the degarelix group compared with the LHRH agonists group (weighted OR: 0.48, 95% CI 0.25 to 0.91, p=0.025).

4.18 The manufacturer also carried out a meta-analysis of adverse events, using data from the CS21, CS28, CS30 and CS31 trials in which monthly degarelix was compared with monthly leuprorelin or goserelin plus bicalutamide. The manufacturer stated that overall there was no

statistically significant difference in the proportion of patients experiencing any adverse events, serious adverse events and discontinuation because of adverse events between degarelix and LHRH agonists groups. The manufacturer noted that the proportion of patients with adverse drug reactions was higher in the degarelix group compared with the LHRH agonists group because of injection site-related adverse events. The most common adverse event in both treatment groups was the rate of hot flushes. The manufacturer also presented pooled analyses of individual patient-level adverse events data from the 6 RCTs (n=2328 patients of which 1491 were in the degarelix group and 837 in the LHRG agonists group [goserelin: n=458; leuprorelin: n=379) which were subsequently used in the economic model. The manufacturer highlighted that among the patients with pre-existing cardiovascular disease, the risk of cardiac events within 1 year of initiating therapy was lower for patient in the degarelix group compared with those in the LHRH agonists group (HR 0.44, 95% CI 0.26 – 0.75, p=0.0023). The probability of joint-related signs and symptoms was significantly lower in the degarelix group (5.3%) compared with the LHRH agonists group (8.1%) (p=0.0116), as well as the probability of fracture (0.9% in the degarelix group compared with 2.3% in the LHRH agonists group, p=0.0234) and the probability of having a urinary tract adverse event (15.0% in the degarelix group compared with 22.3% in the LHRH agonists group, p<0.0001).

4.19 The manufacturer presented evidence from non-randomised studies and extension trials that supported that degarelix was well tolerated and effective in attaining and sustaining suppression of PSA and testosterone levels. The manufacturer included results from the extension trial of CS21 (CS21A), in which all patients who previously received leuprorelin were randomised to 1 of the 2 degarelix groups (160mg or 80mg maintenance dose) and were followed up for 5 years. After a protocol amendment all patients received a monthly degarelix maintenance dose of 80mg. 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 the main CS21 trial. There were no statistically significant differences in the number of patients with PSA progression or who escaped 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 while the rate in those who continued on the degarelix group was consistent with the rate observed in CS21.

4.20 The manufacturer conducted a literature review to carry out a mixed treatment comparison in terms of overall survival to explore whether the previous meta-analyses' findings of similar clinical efficacy between LHRH agonists could be supported and to evaluate the evidence available to compare bicalutamide monotherapy with degarelix (please see page 85 of the manufacturer's submission for further information). The manufacturer only included the RCTs that used the licensed dose of degarelix (240/80mg) and compared 1-monthly dosing regimens (CS21, CS28, CS30 and CS31). The manufacturer identified 2 further studies to be included in the MTC: Heyns et al (2003) which compared triptorelin with leuprorelin in men with advanced prostate cancer, and Iversen et al (1998) which compared daily bicalutamide with surgical castration or monthly goserelin in patients with previously untreated non-metastatic advanced prostate cancer. The results favoured degarelix compared with all other treatments, except when compared with triptorelin (OR 0.505). None of these results showed statistically significance (see table 8) The manufacturer stated that the paucity of evidence to compare bicalutamide with degarelix prevented a robust comparison and that a naïve indirect comparison was not completed as it could provide misleading or biased estimates of treatment effects. In response to clarification, the manufacturer presented results for a modified network of trials comparing 3 interventions: degarelix, LHRH agonists and bicalutamide. The results did not show any statistically significant difference between the interventions (OR of degarelix compared with LHRH agonists: 1.81; 95%

CrI 0.36 – 7.27; and OR of degarelix compared with bicalutamide: 0.77; 95% CrI 0.16 – 15.15).

Table 8 Results of the manufacturer's MTC between degarelix and comparators in terms of overall survival

Comparison (1st vs. 2nd)	OR (95% CrI)
Leuprorelin vs. degarelix	1.765 (0.239 – 13.922)
Goserelin vs. degarelix	1.549 (0.153 – 12.492)
Triptorelin vs. degarelix	0.505 (0.035 – 8.569)
Bicalutamide vs. degarelix	1.58 (0.090 – 21.492)
Leuprorelin vs. goserelin	1.154 (0.068 – 25.18)
Leuprorelin vs. triptorelin	3.443 (0.371 – 31.21)
Leuprorelin vs. bicalutamide	1.133 (0.044 – 39.32)
Goserelin vs. triptorelin	3.027 (0.076 – 86.28)
Goserelin vs. bicalutamide	0.974 (0.131 – 7.899)
Triptorelin vs. bicalutamide	0.322 (0.008 – 18.80)

Source: adapted from manufacturer's submission, figure 15, page 87

4.21 In response to clarification the manufacturer also presented results of a MTC for the rate of hot flushes as the solely safety outcome stating that a MTC for any other efficacy and safety outcomes was impossible as they were measured and reported very differently across trials. The results of this MTC showed no statistically significant differences in the rate of hot flushes between degarelix and the rest of interventions.

Evidence Review Group comments and exploratory analyses

4.22 The ERG considered that the manufacturer's search strategy in the systematic review of the clinical effectiveness was sufficient and it was satisfied that all relevant RCTs were identified for the direct comparison of degarelix with LHRH agonists in combination with 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 with all stages of prostate cancer but acknowledged that in practice it was not possible to limit the population to patients with locally advanced and metastatic prostate cancer in the systematic review as there was no clinical evidence for this population. It therefore considered

that the inclusion criteria for the systematic review conducted by the manufacturer were appropriate.

4.23 The ERG noted that because all RCTs included in the manufacturer's submission included patients with all stages prostate cancer, the generalisability of the results to the target population in this appraisal and therefore, to UK clinical practice could be limited. The ERG considered that it would have been preferable to exclude patients with localised or not classifiable disease from the analyses presented in the manufacturer's submission. It further noted that PSA levels for all trials were lower than what would be expected in clinical practice and that this was likely to be because of the wider inclusion criteria and subsequently lower severity of disease in the trial populations. The ERG heard from clinical specialists that the majority of patients who receive treatment with LHRH agonists will receive anti-androgen flare protection with bicalutamide in the UK and noted that the proportion of patients who received anti-androgen flare protection in the trials was low.

4.24 The ERG noted that the manufacturer used several pooled analyses to present the results from the RCTs and 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 acts independently, minimising the impact of potential confounding variables. Therefore, the ERG considered that the results presented in pooled analyses in the manufacturer's submission were inappropriate and should be interpreted with caution.

4.25 The ERG considered the meta-analyses conducted by the manufacturer. Firstly, it noted that the manufacturer did not provide a justification for the assumption that leuprorelin and goserelin had equivalent efficacy. Secondly, it commented that the results for PSA response showed significant heterogeneity but the manufacturer did not carry out a formal

meta-regression. Furthermore, the ERG noted that the manufacturer included the CS35 trial in some of the meta-analyses, for example, when presenting the results in terms of overall survival. The ERG considered that this trial should have been excluded from these analyses because it used an unlicensed dose of degarelix, and another trial (CS37) had been excluded for use of 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 considered that the hazard ratio (HR) best represented these results. Finally, it concluded that the results for overall survival should be interpreted with caution because the study duration of the included trials was too short and they were not designed to detect differences in survival.

4.26 The ERG considered the MTC presented by the manufacturer for the comparison of degarelix with LHRH agonists (goserelin, leuprorelin and triptorelin) and with bicalutamide. The ERG highlighted that 2 of the studies excluded by the manufacturer could have been appropriate for inclusion (Chodak et al [1995] and Kaisery et al [1995]) because they reported results in terms of overall survival. The ERG commented that it was not possible to assess the suitability for a naïve indirect comparison with bicalutamide because the baseline characteristics from the subgroup of patients with locally-advanced prostate cancer in the CS21 trial were not provided in the manufacturer's submission and therefore, it was unclear how similar the population in the trial was compared with the population included in the study by Iversen et al (1998). The ERG considered further that the manufacturer's conclusion that the non-significant difference in overall survival between LHRH agonists in the MTC demonstrated equivalence in clinical efficacy was not sustained. The ERG commented that the 2 studies cited by the manufacturer to support its statement needed to be interpreted with caution as Hemels et al [2002] had not been published in a peer reviewed journal and Seidenfeld et al [2000] was published before one of the studies included in the MTC

(Heyns et al [2003]) were published. The ERG considered that the results of the MTC suggested that there was a potential difference in overall survival associated with triptorelin when compared with goserelin and leuprorelin.

4.27 The ERG carried out additional work updating the manufacturer's searches and amending the search strategies. The ERG did not identify any additional relevant RCTs that were not already reported in the manufacturer's submission. The ERG also conducted additional analyses in the MTC applying informative priors for the heterogeneity parameter and the baseline treatment effect, but non-informative priors for the treatment effects, and using the time points for overall survival from each of the included trials to present the results in terms of HR. The ERG concluded that these results suggested that there was small heterogeneity between studies and that triptorelin was associated with lower mortality risk than leuprorelin (HR 0.28, 95% CrI 0.07 to 0.95) (see table 9).

Table 9 Results of the ERG's MTC between degarelix and comparators in terms of overall survival

Comparison	Hazard Ratio (95% CrI)
Leuprorelin vs. Degarelix	1.71 (0.51, 6.31)
Goserelin vs. Degarelix	1.59 (0.15, 14.73)
Triptorelin vs. Degarelix	0.48(0.07, 2.79)
Bicalutamide vs. Degarelix	1.63 (0.14, 16.57)
Goserelin vs. Leuprorelin	0.93 (0.07, 11.30)
Triptorelin vs. Leuprorelin	0.28 (0.07, 0.95)
Bicalutamide vs. Leuprorelin	0.96 (0.06, 12.79)
Triptorelin vs. Goserelin	0.30 (0.02, 5.42)
Bicalutamide vs. Goserelin	1.03 (0.49, 2.19)
Bicalutamide vs. Triptorelin	3.48 (0.18, 64.48)

Source: ERG's report, table 26, page 79

5 Comments from other consultees

5.1 The professional groups noted that the current management of advanced hormone-dependent prostate cancer involves treatment with LHRH agonists and that degarelix would be used at the same stage as LHRH agonists in the treatment pathway. They noted that degarelix has a similar

efficacy and safety profile to LHRH agonists which are currently used for treating non-localised prostate cancer. The professional groups stated that in clinical practice, treatment with LHRH agonists or degarelix is continued even if PSA or symptomatic disease progression is observed. The professional groups also noted the availability of anti-androgen treatments such as bicalutamide, which is used as an alternative for patients without metastatic disease and which has the advantage of reduced hot flushes while maintaining sexual interest.

5.2 The professional and patient groups noted that the main advantage from degarelix was the rapidity of its effect without the need for anti-androgen flare cover. They also highlighted that a benefit of degarelix is longer PSA progression-free survival. They commented that the flare associated with LHRH agonists might lead to an exacerbation of bone pain, obstructive outflow symptoms and possibly the development of urinary retention or cord compression. The professional and patient groups noted that degarelix may reduce the risk of further cardiovascular events in men who have had prior cardiovascular disease, and that it might have additional advantages for patients with impeding spinal cord compression (SCC) or who have significant bone pain. The professional groups highlighted that degarelix provides immediate benefit for men with advanced disease and faster symptom control, and that it has shown long term suppression of testosterone for up to 364 days. A professional group stated that the use of degarelix was only justified when rapid androgen ablation is desired.

5.3 The professional and patient groups stated that that there were no additional disadvantages from degarelix compared with LHRH agonists because the side effects were similar. The patient groups noted that the majority of the patients were concerned about potential side effects with degarelix (as hot flushes, weight gain, anaemia, tiredness, bone thinning, breast swelling or tenderness and loss of sex drive and erection problems) but no more so than with any other standard treatment. The patient groups also highlighted the need of considering the management of osteoporosis in the treatment pathway of advanced prostate cancer as

it was a known adverse event from hormonal therapy. The patient groups stated that patients considered that the most common benefits from degarelix were improved survival, providing more treatment options, better quality of life and the rapid effect of degarelix.

5.4 The patient groups noted that the majority of people with prostate cancer were men aged 65 and over and that men from African Caribbean family origin were more likely to develop prostate cancer than men from white family origin groups in the UK. They noted further that people from lower socioeconomic backgrounds have a lower survival rate from prostate cancer and that it will be important to ensure that eligible patient to degarelix have equal access to this technology. The patient groups highlighted that if degarelix is recommended it will help to provide standardised access to the treatment, increasing the range of clinically effective treatment options and providing patients with greater choice.

5.5 The professional groups highlighted that the cost of degarelix is greater than the cost of LHRH agonists. They noted that it is currently available in some secondary care hospitals, but stated that degarelix is administered by subcutaneous injection and that it can be provided in the primary care setting similar to LHRH agonists. The patient groups highlighted that degarelix will reduce hospital and GPs' visits because there is no risk of tumour flare.

6 Cost-effectiveness evidence

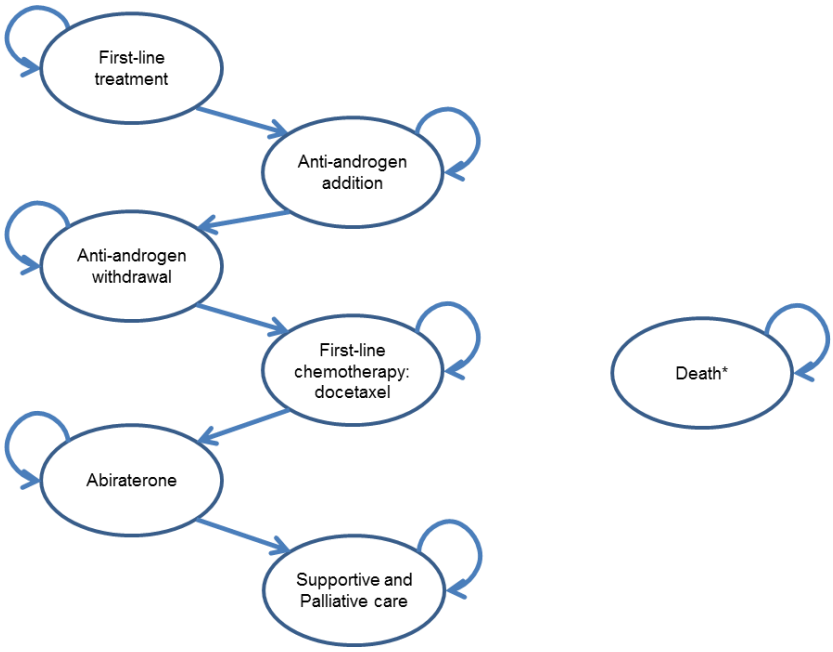
6.1 The manufacturer carried out a systematic review to identify published economic evaluations comparing the use of degarelix with LHRH agonists and androgen antagonists for treating advanced hormone-dependent prostate cancer. Of the 32 publications identified, the manufacturer considered that 3 of them (Lu et al [2011], Lee et al [2012] and Hatoum et al [2013]) were relevant for inclusion (for further details please see the manufacturer's submission, table 59, page 202). The manufacturer concluded that these studies were inadequate to fully inform decision-

making in the UK because: a US perspective was taken in Hatoum et al, the model structure in Lu et al did not account for all of the additional benefits of treatment with degarelix, and the study by Lee et al was only available as a poster and therefore there was a lack of detail on the methods used.

6.2 The manufacturer submitted 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. It also included comparisons between degarelix and other LHRH agonists: leuprorelin and triptorelin plus short-term anti-androgen treatment with bicalutamide. The manufacturer stated that a comparison with bicalutamide monotherapy was not possible because of the lack of clinical evidence to inform this comparison. The model had a cycle length of 4 weeks (28 days) and a lifetime horizon (30 years). The manufacturer stated that the model did not include a half cycle correction because the cycle length was short compared to average survival and it would make no substantial difference to the cost-effectiveness results.

6.3 The Markov model included 7 health states (please see figure 4). The health states mirrored the UK treatment pathway for patients with advanced hormone-dependent prostate cancer, and it was assumed that all patients followed an identical treatment pathway. All patients received treatment with degarelix or LHRH agonists. Following PSA progression the anti-androgen bicalutamide was added followed by a period of anti-androgen withdrawal. Following the end of response to anti-androgen withdrawal treatment with degarelix or LHRH agonists was stopped and all patients received chemotherapy. After chemotherapy, patients received treatment with abiraterone, supportive care and lastly palliative care. It was assumed that all patients received each line of treatment line if they were still alive.

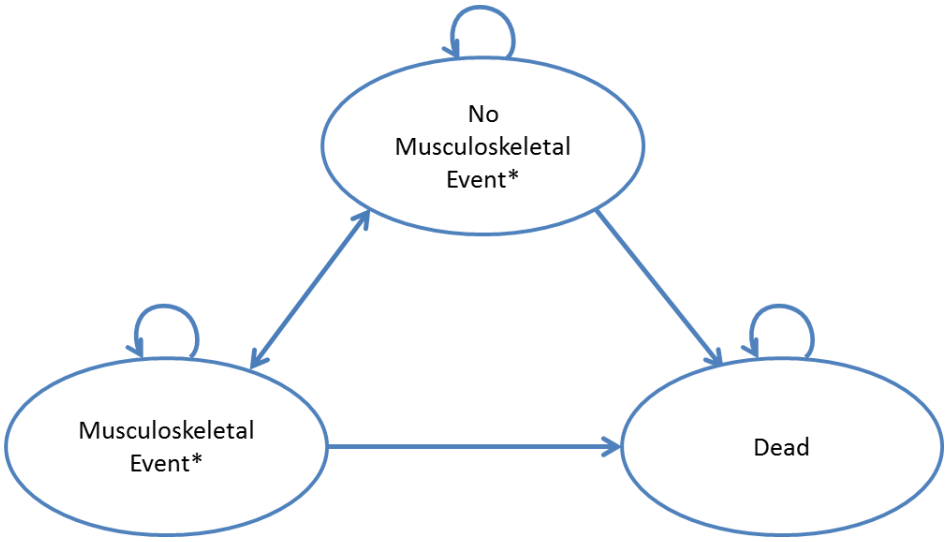
Figure 4 Manufacturer's model structure



Source: Manufacturer's submission, figure 19, page 114

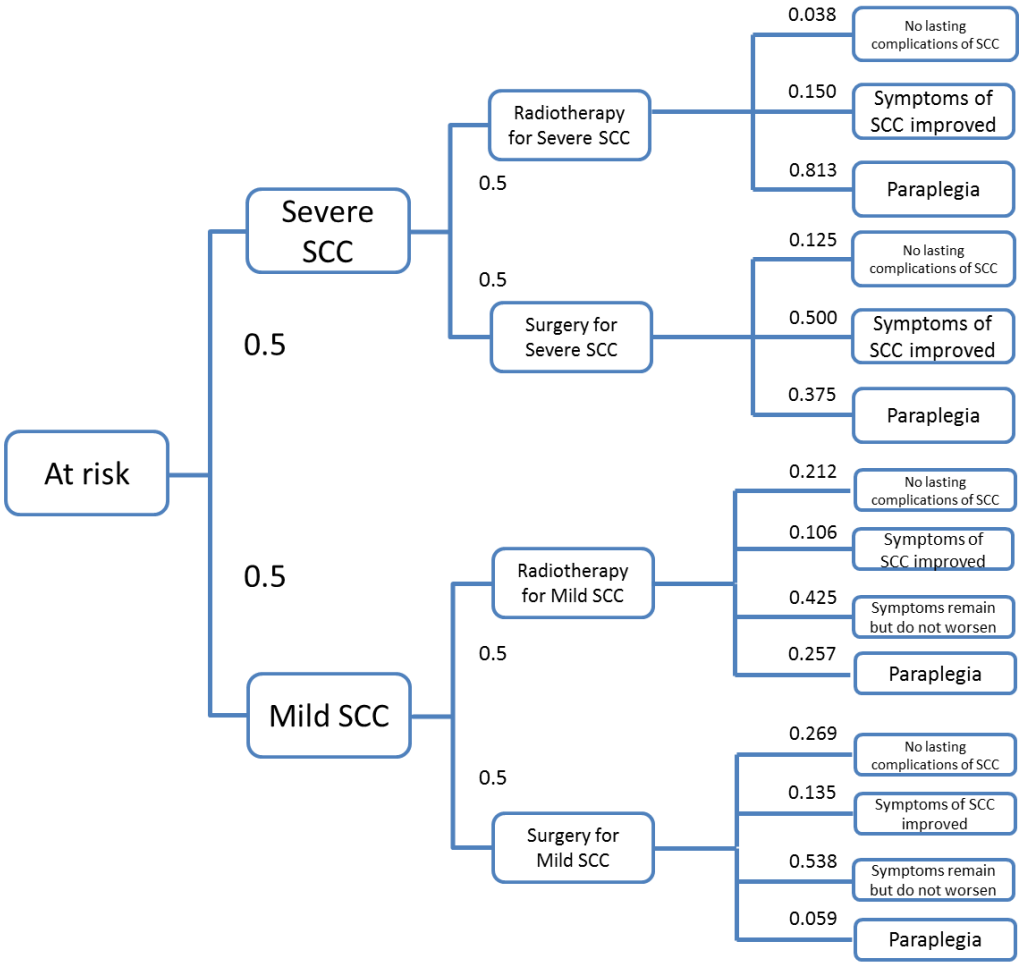
6.4 The manufacturer included 3 sub-models to represent the adequate management of adverse events: musculoskeletal events, spinal cord compression (SCC) events and cardiovascular events (see figures 5, 6 and 7). The manufacturer assumed in the model that patients receiving degarelix and LHRH agonists could have fractures, joint-related signs and symptoms (JSS) and cardiovascular events. In contrast, only patients receiving LHRH agonists could have a SCC event because it was assumed that this event 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 RCTs included in the clinical evidence. Costs and decrements in quality of life were applied to the model for the incidence of these adverse events. The manufacturer did not include the incidence of any other adverse events in the model.

Figure 5 Manufacturer's sub-model structure for musculoskeletal events (fracture or JSS)



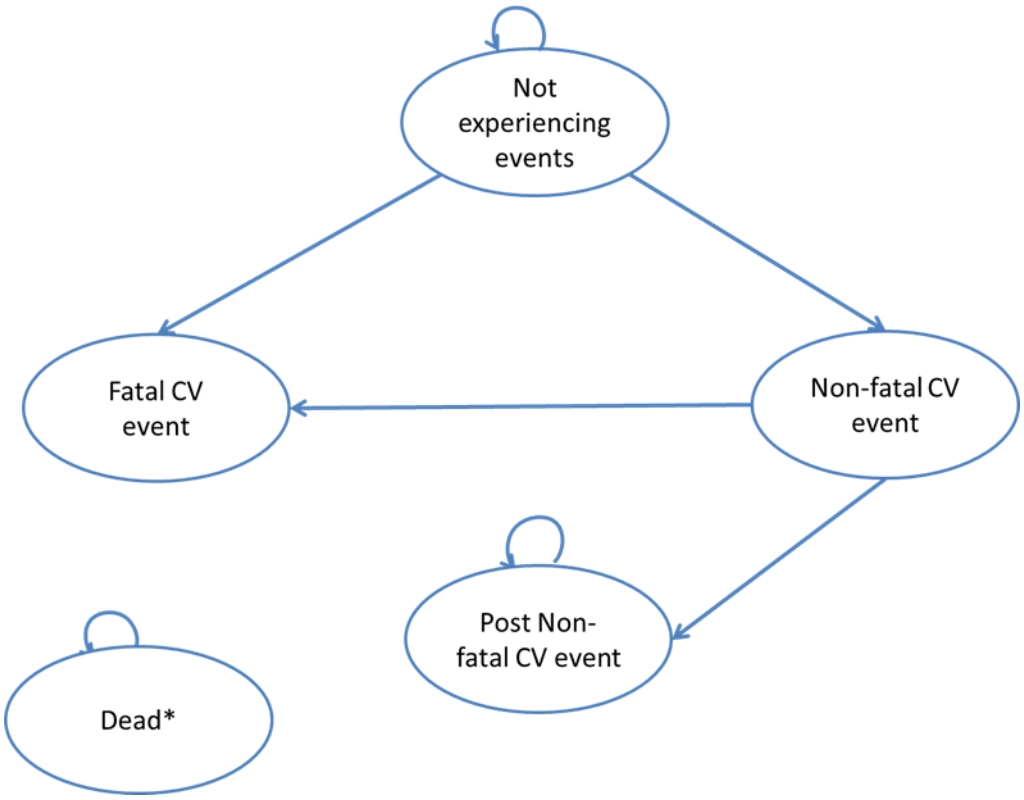
Source: Manufacturer's submission, figure 20, page 115

Figure 6 Manufacturer's sub-model structure for SCC events



Source: Manufacturer's submission, figure 21, page 115

Figure 7 Manufacturer's sub-model structure for cardiovascular events



Source: Manufacturer's submission, figure 22, page 116

6.5 The manufacturer assumed that the efficacy and safety profiles of the LHRH agonists were equal to leuprorelin (the comparator in CS21) and chose goserelin as the comparator for the base case analysis because it was the most commonly prescribed LHRH agonist in England and Wales. The manufacturer based the clinical inputs in the model on the intention to treat population from CS21 and CS21A. It also considered a subgroup from CS21 including patients with PSA levels greater than 20ng/ml which the manufacturer suggested were more reflective of the population receiving hormonal therapy in the UK. It included the comparison with the less and most expensive LHRH agonists in sensitivity analyses. The cost-effectiveness analysis was conducted from a NHS perspective, costs and outcomes were discounted at 3.5% per annum. The manufacturer also assumed in the model that:

- The differential efficacy continued after the trial period

- The efficacy across the different doses of LHRH agonists was equal
- Patients who initially had mild SCC who improved had the same utility as those whose problems were resolved
- Patients with metastatic disease whose disease progressed from first-line treatment had an increased risk of mortality
- Patients who had a non-fatal cardiovascular event did not experience additional utility decrement from 28 days after the event
- Rates of adverse events were not dependent on the dose of degarelix given.

6.6 All patients entered the model in first-line treatment with degarelix or LHRH agonists. PSA progression was used as an indicator for patients moving through the model onto subsequent lines of treatment. The manufacturer stated that, based on expert opinion, PSA progression was a good indicator of biochemical disease progression. The treatment effect from degarelix was derived from the Kaplan-Meier estimated probabilities 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 (defined as PSA greater than 20ng/ml). The manufacturer applied the 1 year treatment effect observed in CS21 to the parametric curves assuming proportional hazards (see table 10). It also explored the sensitivity of the model results to the proportional hazards assumptions in a sensitivity analysis.

Table 10 Treatment effect for degarelix assumed in the manufacturer's model

Population	Hazard ratio (95% CI)	p-value
ITT	1.71 (1.00-2.93)	0.05
PSA>20 ng/ml	1.74 (0.99-3.07)	0.05
CI = confidence interval; ITT = intention-to-treat; PSA = prostate-specific antigen.		

Source: Manufacturer's submission, table 24, page 125

6.7 The manufacturer modelled patient progression through subsequent lines of treatment 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 EAU guidelines. Mean duration of response to treatment with abiraterone was taken from abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen (NICE Technology appraisal guidance 259) (see table 11). It was assumed that after anti-androgen withdrawal, all patients will have metastatic disease.

Table 11 Duration of response to subsequent lines of therapy

Treatment line	Mean duration of response (months)
Anti-androgen addition	6.0
Anti-androgen withdrawal	6.0
Docetaxel	12.0
Abiraterone	6.45

Source: Manufacturer's submission, table 25, page 125

6.8 Survival data 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 investigated the fit of different parametric curves to be used to estimate the extrapolation of the additional mortality above the rate that would be expected on the basis of the general population mortality rates. The manufacturer chose a log-logistic distribution because this produced the lowest mean absolute error compared with the observed data. The manufacturer generated separated survival curves for patients with metastatic disease and non-metastatic disease assuming that 9.4% of the population with prostate cancer in the Scottish Cancer Registry had metastatic disease based on the estimates from abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen (NICE technology appraisal guidance 259) and prostate cancer prevalence figures obtained from the National Cancer Intelligence Network. Therefore, patients in the model faced different hazards for mortality as they progressed through each line of 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 stated that adding the link between progression

from first-line treatment (based on PSA progression) and an increased risk of mortality for patients with metastatic disease had the effect that of delayed progression from the first-line treatment states resulted in a lower mortality risk. This assumption was supported by the study of Hussain et al (2009) in which it was shown that PSA progression, defined as an increase of 25% or more over the lowest PSA level and an absolute increase of 2 or 5ng/ml or more, predicted overall survival. The manufacturer suggested that using data from CS21 overestimated the proportion of patients with localised disease and that 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 lower mortality risk to patients with metastatic disease receiving abiraterone based on NICE technology appraisal guidance 259 and a reduced risk of death for patients receiving degarelix who had a cardiovascular event because this risk is assumed to be already captured in the relative prostate cancer mortality rates.

Adverse events

6.9 The manufacturer chose the Weibull distribution as the best fit for the hazard of experiencing a musculoskeletal event because the data showed that this hazard was not constant over time. The hazard of having a JSS event decreased over time for both treatment arms and the hazard of having a fracture decreased over time for degarelix but increased for LHRH agonists. The manufacturer applied long-term quality of life and cost decrements for patients who remained in pain for severe JSS and severe fractures based on the proportion of patients remaining in pain each cycle from Hollingworth et al (2008). The risk of having a SCC was taken from the study of Lu et al and the mortality risk of patients having this adverse event was assumed to be similar to the rest of the patient population in the model.

6.10 The manufacturer applied exponential distributions to the probability of having a cardiovascular event from the pooled trial data because the data did not contradict the assumption of constant hazards. It noted that it only applied the risk of having a cardiovascular event to those patients who had a cardiovascular event at baseline (30.6% of the patients) because the pooled trial data only indicated a statistically significant difference between degarelix and leuprorelin for these patients. The manufacturer used separated curves to account for fatal and non-fatal events and assumed that patients who had a cardiovascular event needed to be managed for this condition for the duration of the model.

Utility values

6.11 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 review carried out by the manufacturer indicated that as patients progressed to subsequent lines of treatment their health related quality of life decreased. The manufacturer applied different mapping algorithms to transform health-related quality of life data obtained with the SF12 v2 (using the algorithm from the Health Economics Research Centre based on Gray et al [2004]) and EORTC QLQ-C30 (using the algorithms from Kontodimopoulos et al [2009] and from McKenzie and van der Pol [2009]) questionnaires used in CS21 into utility values based on the EQ-5D questionnaire. The manufacturer chose to use the utility values obtained with the mapping algorithm by Kontodimopoulos et al where possible in the economic analysis because this algorithm was derived from patients with a less severe and comparable condition to that of the patients with advanced hormone-dependent prostate cancer in CS21. The difference in utility values between treatment arms was not statistically significant (p=0.27) when using the Kontodimopoulos et al algorithm. Utility decrements associated with adverse events were also applied in the model. The manufacturer included the utility values obtained using other mapping algorithms and other sources of utility values identified in the literature review in sensitivity analyses (please see manufacturer's

submission, table 59 page 202). Table 12 shows a summary of utility values used in the economic model.

Table 12 Summary of utility values used in the economic model

State	Utility value	Confidence interval	Justification
First-line treatment	0.887	(0.879–0.894)	Mapping algorithm produces an EQ-5D based utility in line with the reference case
Anti-androgen addition	0.753	(0.697–0.806)	Mapping algorithm produces an EQ-5D based utility in line with the reference case
Anti-androgen withdrawal	0.753	(0.697–0.806)	Assumed the same as for anti-androgen addition based upon Bayoumi *et al*
First-line chemotherapy	0.689	(0.686–0.692)	Study using the EQ-5D identified using the literature search. Study by Bahl *et al* chosen as included UK patients and had a large number of patients.
Palliative care	0.551	(0.527–0.580)	Study using the EQ-5D identified using the literature search. Study by Sanbolm *et al* chosen as included European patients.
Adverse events*			
Severe SCC	0.195	(0–0.390)	Used by Lu *et al* in earlier analysis
Mild SCC	0.370	(0.270–0.470)	Used by Lu *et al* in earlier analysis
Fracture	0.533	(0.19–0.88)	Mapping algorithm produces an EQ-5D based utility in line with the reference case
Joint-related signs and symptom	0.816	(0.75–0.90)	Mapping algorithm produces an EQ-5D based utility in line with the reference case
Non-fatal CV event	0.803	(0.66–0.94)	Mapping algorithm produces an EQ-5D based utility in line with the reference case

Key: CV cardiovascular; EQ-5D = EuroQol five-dimensions; HRQL = health-related quality of life; SCC = spinal cord compression
* The value shown for the adverse events is the utility value when on first-line treatment. In later lines of treatment the value is calculated by taking the given adverse event value in first line and multiplying it by the ratio between the HRQL value in the first line of treatment and the HRQL value in the line of treatment the patient is in (e.g. HRQL of a patient with severe SCC when on chemotherapy = 0.2*(0.67/0.887))
Source: adapted from manufacturer's submission, table 41, page 163.

Resource use and costs

6.12 The manufacturer also carried out a literature review to identify cost and resource use studies in patients with advanced prostate cancer and 11 studies met the inclusion criteria. Drug costs were taken from public

sources (the British National Formulary [BNF] 65th edition and Commercial Medicines Unit – Electronic Marketing Information tool [eMIT]). The manufacturer assumed that drug administration was provided in the primary care setting in 50% of cases and the secondary care setting (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 an urologist every 6 months, at which time a PSA test was administered. The costs of adverse events were calculated based on NHS reference costs and PSSRU costs and from the published literature. Costs of supportive and palliative care were also included in the model. The manufacturer stated that all these costs and resource use were validated by UK clinicians.

Results

6.13 Results from the manufacturer's base-case analyses are presented in table 13. These results showed that degarelix was a dominant alternative (that is, it has lower costs and better outcomes compared with the alternative intervention) compared with goserelin for treating advanced hormone-dependent prostate cancer.

Table 13 Manufacturer's base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Goserelin (10.8 mg)	£27,636	9.21	5.28				
Degarelix	£25,939	9.58	5.86	-£1,697	0.37	0.58	Dominating

Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALYs = quality-adjusted life-years
Source: Manufacturer's clarification response, appendix 9, table 7

6.14 The manufacturer also presented results of subgroup analyses for patients at high risk of disease progression (PSA levels at baseline greater than 20ng/ml) and for those patients with cardiovascular disease at baseline. Results are presented in Tables 14 and 15 respectively.

Table 14 Manufacturer's results for the high-risk population (PSA>20ng/ml)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Goserelin (10.8 mg)	£29,794	4.77	8.78				
Degarelix	£28,104	5.36	9.22	-£1,691	0.59	0.44	Dominating

Key: ICER =incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life-years
Source: ERG's report, table 39, page 108

Table 15 Manufacturer's results for the subgroup of patients with cardiovascular disease at baseline

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Goserelin (10.8 mg)	£24,492	7.22	4.23				
Degarelix	£28,104	9.58	5.86	£6856	2.36	1.63	£4216

Key: ICER =incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life-years
Source: ERG's report, table 40, page 108

The manufacturer undertook sensitivity analyses to explore the impact of changes in the base-case assumptions and parameters in the cost effectiveness results. The results showed that the model was most sensitive to the hazard of PSA progression. The manufacturer also conducted several scenario analyses varying the assumptions in the model. The highest ICER in the manufacturer's sensitivity analyses was equal to £11,274 per additional QALY. This scenario showed the results when assuming the efficacy of degarelix to be equal to LHRH agonists. For full details of the results of the manufacturer's sensitivity analyses please see manufacturer's response to clarification, appendix 9, table 8.

6.15 The manufacturer also undertook probabilistic sensitivity analyses to explore uncertainty around the parameters in the model. As response to clarification, the manufacturer updated the probabilistic sensitivity analyses applying lognormal distributions for some HR and unit cost parameters which had been previously represented using uniform distributions. 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 drivers of the cost-effectiveness results were the higher efficacy and safety profile of degarelix. It stated that the increased time to PSA progression achieved with degarelix resulted in a higher patient health-related quality of life, reduced hazard of mortality and reduced time on abiraterone. The manufacturer also added that the more favourable efficacy profile of degarelix resulted in higher patient health-related quality of life, reduced mortality from cardiovascular events and cost-offsets because of the avoidance of costs associated with managing adverse events.

Evidence Review Group comments and exploratory analyses

6.16 The ERG agreed that published cost-effectiveness analyses were not relevant to the decision problem for this appraisal and therefore a de novo economic evaluation was appropriate. Following clinical advice, the ERG considered that the treatment pathway presented by the manufacturer and replicated in the economic model differed from the treatment pathway observed in UK clinical practice. It noted the manufacturer's assumption that patients will receive treatment with degarelix or LHRH agonists until the disease progressed and became hormone refractory. The ERG noted that the summary of product characteristics states that patients must have hormone-dependent disease to start treatment with degarelix or LHRH agonists, but that these treatments do not need to be stopped after disease progression. The ERG supported this assumption based on expert opinion, stating that in clinical practice, treatment with degarelix or LHRH agonists will be continued until death. The ERG also suggested that it was more appropriate to use the data from all the relevant RCTs instead of using only the results from CS21 in the economic model.

6.17 The ERG noted that the manufacturer's base case analysis included a comparison between degarelix and goserelin, and that comparisons with other LHRH agonists were explored in sensitivity analyses. The ERG

suggested that the lowest cost brand of goserelin, should have been excluded from the economic analysis because this drug was no longer in production. The ERG believed that the assumption of equivalent efficacy between all LHRH agonists was unjustified 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 MTC presented by the manufacturer did not include any RCTs that directly compared degarelix with bicalutamide, an indirect comparison could have been conducted based on the results from Iversen et al (2008) and used in the economic model for those people with locally advanced prostate cancer. The ERG stated that it was unable to carry out this comparison because of limitations on the manufacturer's model structure.

6.18 The ERG noted that the benefit of degarelix compared with LHRH agonists in terms of PSA progression had only been shown for a period of 1 year (the duration of CS21) and that it was unknown whether this treatment effect would be maintained after this period. Therefore the ERG suggested that this relative treatment effect should only be applied in the model during 1 year, and that equivalent efficacy between treatment arms should be assumed after that.

6.19 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 the short duration of the clinical trials, it was not possible to demonstrate a clinical benefit from degarelix compared with LHRH agonists in terms of overall survival. The ERG suggested that it would be more appropriate to consider that the treamtment benefit from degarelix was only derived by a benefit in terms of PSA progression but no relationship between PSA progression and overall survival should be assumed and that a model structure which explicitly estimates time to metastatic disease and time to death would be more transparent, appropriate and flexible. The ERG stated that it was unable to conduct an exploratory analysis which did not assume any relationship between PSA progression and overall survival because of limitations on the

manufacturer's model structure. The ERG carried out an exploratory analysis that assumed overall survival in patients with metastatic disease was not influenced by progression from first-line treatment.

6.20 The ERG considered that the Weibull distributions applied to the rates of adverse events in the economic model provided a poor fit and that other parametric curves should have been considered. The ERG suggested, based on advice from clinical specialists' that the rate of fractures would likely increase over time for both treatment groups and not just for LHRH agonists because suppressed testosterone levels would lead to a reduction in bone mineral density over time and therefore this assumption should have been applied in the economic model.

6.21 The ERG carried out additional work and presented an updated treatment pathway based on expert opinion which highlighted the following differences: it is usual for treatment with degarelix and LHRH agonists to be continued until death, rather than stopping treatment when chemotherapy commences. Radical local treatment with surgery or radiotherapy will fail in a proportion of patients and they will receive hormone based treatment. The proportion of patients receiving chemotherapy varies between 30 to 70%. Not all patients receive abiraterone and this drug would also be provided before or as an alternative to chemotherapy. Enzalutamide may be used after chemotherapy, and in the elderly watchful waiting may be appropriate.

6.22 The ERG considered that the manufacturer's economic model had several limitations and did not include an unbiased estimate of the ICER for degarelix in comparison with LHRH agonists. It conducted several exploratory analyses varying assumptions and parameters in the model. It suggested that the most plausible scenario will assume:

- 3-mothly triptorelin as the most appropriate comparators because it was the cheapest LHRH agonist

- treatment with degarelix and LHRH agonists continued until death in line with clinical practice and licensed indications
- different treatment effect from degarelix compared with LHRH agonists applied only during 1 year in line with the evidence from CS21
- the proportion of patients receiving chemotherapy after PSA progression was 70% and the proportion of patients receiving abiraterone was 70%.

The results of the ERG's most plausible scenario showed that degarelix provided an additional 0.247 QALY gained when 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, using as a reference its most plausible scenario, and concluded that the cost-effectiveness results were most sensitive to: the exclusion of SCC 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 equal efficacy of degarelix and LHRH agonists. These results are summarised in table 16.

Table 16 Summary of ERG's exploratory analyses

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
ERG's most plausible scenario							
Triptorelin 3 monthly (Decapeptyl)	£22,649	9.39	5.570				
Degarelix	£26,308	9.55	5.818	£3659	0.16	0.247	£14,798
SCC excluded from the analysis							
Triptorelin 3 monthly (Decapeptyl)	£20,785	9.39	5.601				
Degarelix	£26,308	9.55	5.818	£5523	0.16	0.217	£25,486
Same rate of fractures for both treatment arms							
Triptorelin 3 monthly (Decapeptyl)	£22,649	9.39	5.570				
Degarelix	£27,214	9.55	5.778	£4565	0.16	0.208	£21,950

Patients with metastatic disease whose disease progressed from first-line treatment had no increased risk of mortality							
Triptorelin 3 monthly (Decapeptyl)	£24,021	9.97	5.745				
Degarelix	£27,588	10.03	5.954	£3567	0.07	0.209	£17,067
Efficacy of degarelix and LHRH agonists assumed to be equal							
Triptorelin 3 monthly (Decapeptyl)	£22,142	9.49	5.701				
Degarelix	£26,308	9.55	5.818	£4166	0.05	0.117	£35,589

Key: ICER =incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life-years
Source: adapted from ERG's report, tables 43 and 44, pages 115 – 117

6.23 The ERG undertook exploratory analyses for patients with spinal metastasis with actual or SCC, as expert opinion suggested that this subgroup could potentially benefit more from treatment with degarelix. Due to lack of data to conduct this exploratory analysis, the ERG assumed that patients receiving degarelix will not have a SCC event and that the efficacy of degarelix and LHRH agonists in terms of PSA progression and overall survival was equal. The ERG stated that because the rate of SCC events in this subgroup was unknown it presented the results using different values. The ERG noted that based on the assumption of equal effectiveness in terms of PSA progression and overall survival between degarelix and LHRH agonists, the QALY gain associated with degarelix will be higher than with triptorelin because patients receiving degarelix will not be affected by a lower utility associated with SCC events. The ERG concluded that if the rate of SCC events in this subgroup was higher than 3.5%, degarelix would be dominant compared with triptorelin.

7 Equality issues

7.1 During consultation on the draft scope and the scoping workshop discussion, consultees noted that prostate cancer is more common in older men and African Caribbean men are at increased risk compared with white men of the same age in the UK. Because no evidence was

received of differential access to therapy or prognosis in these groups, it was agreed in the scoping workshop that access to degarelix should not be defined by any of the protected characteristics outlined in the current equalities legislation.

7.2 Although the UK marketing authorisation of degarelix is for ‘adult male patients’, it was agreed that the population in the scope should be amended to ‘adults’ because people who have undergone male to female gender reassignment can still develop prostate cancer.

8 Innovation

8.1 The manufacturer stated that degarelix delivers innovation in a variety of ways and can be considered 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 is associated with fewer cardiovascular events. The manufacturer concluded that all relevant health-related benefits associated with degarelix are included in the QALY calculation.

9 Authors

Pilar Pinilla-Dominguez
Technical Lead(s)

Fay McCracken
Technical Adviser

with input from the Lead Team (John Henderson, Gillian Ells and John Dervan).

Appendix A: Supporting evidence

Related NICE guidance

- Prostate cancer: diagnosis and treatment. NICE clinical guideline 58 (2008).
- Urological Cancer. Cancer Service Guidance (2008).

NICE pathways

- There is a NICE pathway on prostate cancer, which is available from http://pathways.nice.org.uk/pathways/prostate-cancer

Appendix B: European public assessment report

The European public assessment report for degarelix was published on 4 March 2013 and is available from:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000986/human_med_000794.jsp&mid=WC0b01ac058001d124