Evidence Review Group's Report

Degarelix for treating advanced hormone-dependent prostate cancer

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Contributions of authors

Lesley Uttley acted as project lead and systematic reviewer on this assessment; critiqued the manufacturer's definition of the decision problem; led the critique of the clinical effectiveness methods and evidence and contributed to the writing of the report. Sophie Whyte acted as health economist on this assessment, critiqued the manufacturer's economic evaluation and contributed to the writing of the report. Tim Gomersall also acted as a systematic reviewer, critiqued the description of the underlying health problem and contributed to the critique of the clinical effectiveness methods and writing of the report. Shijie Ren acted as the statistician on this assessment and contributed to the writing of the report. Ruth Wong critiqued the searches included in the manufacturer's submission and contributed to the writing of the report. Paul Tappenden acted as a senior health economist on this assessment and critiqued the report. Noel Clarke, David Bottomley and Derek Rosario acted as clinical advisors on this assessment and provided input on the current treatment pathway and critiqued the evidence of the clinical effectiveness methods; reviewed and provided comments on the report.

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AE	Adverse event
ADR	Adverse drug reaction
ADT	Androgen deprivation therapy
ALP	Alkaline phosphatase
ANCOVA	Analysis of covariance
BNF	British National Formulary
BPHII	Benign Prostatic Hyperplasia Impact Index
CI	Confidence interval
Crl	Credible interval
CVD	Cardiovascular disease
EAU	European Association of Urology
ECOG	Eastern Cooperative Oncology Group performance status score
EMA	European medicines agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FAS	Full analysis set
FDA	Food and drug administration
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone antagonist
IMP	Investigational medicinal product
IPSS	International prostate symptom score
IR	Interquartile range
ITT	Intention to treat
IU/l	International units per litre
LHRH	Luteinizing hormone-releasing hormone agonists
LOCF	Last observation carried forward
LUTS	Lower urinary tract symptoms
OC	Observed case
ONS	Office for National Statistics
OS	Overall survival
PFS	Progression free survival
PP	Per protocol
PSA	Prostate-specific antigen
PSS	Personal social services

QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
S-ALP	Serum alkaline phosphatase
SAP	Statistical analysis plan
SCC	Spinal cord compression
SD	Standard deviation
SE	Standard error
SF-12 v2	Short form- 12 item survey version 2
SF-36 v2	Short-form- 36 item survey version 2
SFI	Sexual function inventory
SMQs	Standardised MedDRA Queries
SPC	Summary of product characteristics
STA	Single Technology Appraisal
TNM	Tumour node metastasis
TRUS	Transrectal ultrasound
VAS	Visual analogue scale

1 SUMMARY

1.1 Scope of the manufacturer submission

The decision problem addressed in the manufacturer submission (MS) was in line with the final scope issued by the National Institute for Health and Care Excellence (NICE) for degarelix for the treatment of hormone-dependent prostate cancer.

The target population was adult men with advanced hormone-dependent prostate cancer which includes both locally advanced and metastatic disease. However, the available data submitted for this single technology appraisal (STA) included patients with localised and unclassifiable prostate cancer.

The intervention drug Degarelix (Firmagon®) is licensed for use in the UK for a 240mg initiation dose, followed by 80mg monthly doses via subcutaneous injection. The clinical evidence considered in the MS was in line with this indication.

The comparators included the luteinizing hormone-releasing hormone (LHRH) agonist drugs: leuprorelin; goserelin and triptorelin, which are commonly used in clinical practice to treat hormone-dependent prostate cancer in the target population. These agents are commonly combined with an anti-androgen, such as bicalutamide, to protect against the initial flare in testosterone levels that is associated with LHRH agonists. The final NICE scope also indicated that bicalutamide monotherapy should be considered as an appropriate comparator. However, the MS excluded bicalutamide in the base case on the basis that a) bicalutamide monotherapy is only used in locally advanced, not metastatic patients, and so is only of relevance to a subset of the population, and b) there was a lack of trial data directly comparing degarelix with bicalutamide. However, comparisons of bicalutamide monotherapy versus LHRH agonists were identified for overall survival and presented in the MS. Two clinical advisors to the ERG considered bicalutamide monotherapy to represent a relevant comparator to degarelix whilst one clinical advisor considered bicalutamide monotherapy to be used rarely in clinical practice. The ERG believes that it may have been possible to make naïve indirect comparisons of bicalutamide versus degarelix for selected outcomes using data for the locally advanced subgroups within the degarelix trials.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

1.2.1. Clinical effectiveness: degarelix versus comparators

The MS identified six relevant randomised controlled trials (RCTs) of degarelix versus leuprorelin (two trials) and goserelin (four trials), ranging in duration from 3 to 14 months. Four of the trials used the licensed dose of degarelix (240mg followed by monthly maintenance doses of 80mg); whilst two trials used unlicensed 3- or 6-monthly dose schedules, which limits the relevance of these trials to the decision problem. Sample size in the RCTs ranged from 42 to 859. The main pivotal trial of degarelix (CS21), which had a primary endpoint of probability of testosterone levels ≤0.5 ng/ml from Day 28 to Day 84, showed that degarelix (240/80 mg) is non-inferior to leuprorelin (7.5mg). Additionally degarelix achieved a more rapid suppression of prostate-specific antigen (PSA) levels (median reduction at Day 28) than leuprorelin ($p<0.0001$) in trial CS21.

Pooled analyses for: testosterone response; PSA progression-free survival; serum alkaline phosphosphatase; and adverse events using different combinations of the 6 RCTS using simple pooling should be interpreted with caution. In addition, the MS conducted post-hoc analyses on PSA results from one pivotal trial (CS21), and pooled data from this trial with a trial that using an unlicensed intermittent dose of degarelix (CS35) to draw conclusions about degarelix versus comparators plus flare protection. Data were not meta-analysed and the ERG considers that simple pooling assumes that there is no difference between individual studies which may yield counterintuitive or spurious results due to a phenomenon known as Simpson's paradox

Meta-analyses were performed for: reduction in prostate size; change in international prostate symptom score (IPSS); PSA change from baseline; and overall survival. The mortality results favoured degarelix however, the result only became statistically significant when results from the CS35 trial, which used an unlicensed 3-monthly dose of degarelix, were included.

1.2.2. Mixed-treatment comparison

The manufacturer conducted a mixed treatment comparison (MTC) meta-analysis for degarelix with goserelin, leuprorelin, triptorelin, and bicalutamide. The MS reports that due to lack of usable data on other outcomes, overall survival was the only outcome analysed in the MTC. Two additional relevant studies from published papers of the comparators were identified for the MTC. One published study compared bicalutamide monotherapy (150 mg) versus castration (medical or surgical) and one study compared triptorelin with leuprorelin. Both studies were added to four of the degarelix trials (CS21, CS28, CS30, CS31). No

statistically significant differences were found for overall survival in the MTC however the forest plot in the MS showed that leuprorelin and goserelin were associated with increased mortality compared to degarelix whereas mortality for triptorelin appeared lower than degarelix.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG is satisfied that all relevant RCTs were included in the clinical effectiveness review for degarelix. As patients with localised and not classifiable prostate cancer were included in the six RCTs of degarelix, the trial population is not entirely reflective of the target population for which degarelix is indicated. In addition, testosterone flare protection was inconsistently used for patients in the comparator arms, with two trials in particular providing flare protection at a much lower level than would be expected in current UK clinical practice.

Trials CS35 and CS37 were excluded for some analyses on the basis of using unlicensed dosing regimens but subsequently, trial CS35 was included for selected analyses without sufficient justification.

The manufacturer conducted simple pooled analyses instead of meta-analyses from the degarelix RCTs for several outcomes including testosterone response and PSA response. Simple pooling ignores the characteristics of individual studies and relies on the assumption that there is no difference between individual studies. Consequently, the results of such analyses should be interpreted with caution.

The results of meta-analyses should also be interpreted with caution. The IPSS and prostate size outcomes only compared degarelix against goserelin and therefore the conclusion stated by the manufacturer about degarelix versus LHRH agonists is too broad. Similarly, meta-analyses of overall survival and PSA response only compare against leuprorelin or goserelin and therefore conclusions about all LHRH agonists cannot be drawn. Statistically significant heterogeneity was reported for the PSA response meta-analysis and no formal meta-regression was performed to justify this.

The manufacturer claimed that although the hazard ratio of overall survival is the most desirable outcome statistic there was no sufficient data available from the RCTs therefore an odds ratio was used (MS page 85). However, as the duration of each study has been provided this information could be used in the analysis to produce a hazard ratio.

The MTC is limited to the overall survival outcome. The ERG considers that it may not be appropriate to compare these treatments solely on the basis of this outcome in the MTC

because the time horizon of the studies was short, and none were powered to detect differences in survival in this population.

1.4 Summary of cost effectiveness submitted evidence by the manufacturer

The manufacturer's systematic review of cost effectiveness studies identified and reviewed three relevant studies. The review concluded that a *de novo* model was required. A *de novo* Markov treatment-sequence model developed in Microsoft® Excel to estimate the costs and benefits of degarelix treatment over a lifetime horizon for patients with advanced hormone-dependent prostate cancer. The model takes a National Health Service (NHS) and personal social services perspective (PSS) with a time horizon of 30 years and a discount rate of 3.5% applied to both costs and quality-adjusted life years (QALYs). The economic model compares treatment with degarelix to treatment with goserelin 10.8mg (Zoladex) in the base case with comparisons with goserelin (Novgos) and triptorelin (Gonapeptyl) included as scenario analyses.

The manufacturer's model assumes that all patients receive each of the following treatment lines if still alive: first line treatment with degarelix/LHRH agonists; anti-androgen addition; anti-androgen withdrawal; chemotherapy; abiraterone; supportive care; and palliative care. The health-related quality of life (HRQoL) associated with each disease state either falls or remains constant as patients progress. HRQoL data available from the CS21 clinical trial were mapped to EQ-5D. The model states also capture the treatment costs; administration costs; and monitoring costs associated with each of the treatments in the pathway. The modelling includes the following adverse events: fractures; joint-related signs and symptoms; cardiovascular events; and spinal cord compression (SCC) and their impacts on: cost; HRQoL; and mortality.

Transition from first line treatment is based on data for PSA progression with degarelix and LHRH agonists. The model assumes that each of the LHRH agonists have equivalent efficacy. The model uses data from the CS21 and CS21A clinical trials which compare degarelix to leuprorelin for a period of one year before crossover for all patients to degarelix was allowed. A hazard ratio for PSA progression of 1.71 (1.74) for leuprorelin compared to degarelix for the ITT population (PSA>20ng/ml population) was estimated from the CS21 and CS21A trial data. PSA progression for degarelix was modelled via a log-normal distribution. The hazard ratios were applied to the parametric curve fits assuming proportional hazards. Two scenario analyses were also presented: (1) the efficacy of degarelix and LHRH agonists were assumed equal and; (2) the efficacy of degarelix and LHRH agonists were assumed equal after 1 year.

Duration of response to subsequent lines of treatment is based on estimated response durations reported in the European Association of Urology (EAU) guidelines. Mortality rates which are age specific and dependent on the presence of metastatic disease were derived from ONS data and Scottish prostate cancer mortality data. Mortality for patients on first line treatment was calculated based on the proportions of patients with localised, locally – advanced and metastatic disease from the CS21 trial. Patients in the health states: chemotherapy; abiraterone; and supportive/palliative care were assumed to have metastatic disease so this mortality rate was applied. However, a different mortality rate was applied for patients receiving abiraterone. An increased hazard of mortality was applied for patients with metastatic disease once they had progressed from first-line treatment.

The MS base case analysis for degarelix compared to triptorelin (3-monthly) resulted in a cost saving of £1,223 and a QALY gain of 0.58 so degarelix dominated. The cost saving is due to a reduction in subsequent-line therapies and cardiovascular/musculoskeletal events compared with LHRH agonists. A subgroup analysis for patients with PSA>20ng/ml resulted in a cost saving of £1,489 and a QALY gain of 0.44 A subgroup analysis for patients with baseline cardiovascular disease resulted in incremental costs of £6,856, incremental QALYs of 1.63 and an ICER of £4,216 per QALY.

A series of sensitivity analyses were undertaken to test structural assumptions. The assumptions which had the greatest impact on the ICER were:

- Efficacy of degarelix and LHRH agonists assumed to be equal: £12,987 per QALY
- Hazard ratio for differential efficacy between degarelix and LHRH agonists applied for one year (the duration for which there is comparative trial data): £3,751 per QALY
- The exclusion of musculosketal adverse events from the model: £2,484 per QALY
- The exclusion of abiraterone: £2,072 per QALY

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The submission was considered to be complete with regard to relevant published cost-effectiveness studies. The *de novo* economic model adequately addresses the NICE reference case. The ERG believe that the *de novo* economic evaluation had several significant limitations and that the MS does not contain an unbiased estimate of the technology's ICERs in relation to relevant populations, interventions comparators and outcomes. These limitations are discussed in turn.

Clinical advice received by the ERG states that there is variation in the treatment sequence between patients, so the 'treatment sequence' model structure used is inappropriate. The ERG considers that a model structure that explicitly models time to metastatic disease and time to death and allows variation in treatment sequences would be more appropriate, flexible and transparent. The ERG believes that the assumption that treatment with degarelix/LHRH agonists would stop when treatment with chemotherapy begins differs to clinical opinion so should not be used as base case assumption. The ERG suggests that even with the lack of evidence it may be worthwhile to consider subgroups in exploratory analyses. For example, clinical advice suggests that there may be considerable additional benefit in avoiding flare and associated adverse events in the subgroups 'patients with spinal metastases with impending or actual spinal cord compression' and 'patients with high tumour volume with impending or actual urinary outflow obstruction.

A comparison with all the LHRH agonists should have been presented however this was provided following request for clarification from the ERG. The ERG suggests that the inclusion of an analysis comparing degarelix to bicalutamide monotherapy would be useful. The ERG believes that it is inappropriate to assume equal efficacy for each of the LHRH agonists. The economic model should include all relevant trial data rather than the reliance on only one trial. The scenario analyses included in the MS with relation to efficacy assumptions are appropriate and useful. The ERG believes that the uncertainty in HRQoL values has been adequately represented by the scenario analyses included within the MS. The costs used within the economic model are clearly described with the exception of the costs of treating SCC which are not well reported.

The set of sensitivity analyses presented in the MS address many of the key areas of structural uncertainty within the model. The model used to undertake the PSA was not provided by the manufacturer so could not be checked by the ERG. The model validation undertaken by the manufacturer was not comprehensive. In particular, the health professionals who were consulted by the manufacturer did not review the viability of the extrapolation of adverse event data beyond the clinical trial period.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

The ERG identified a number of strengths in terms of the robustness of evidence in the submission, including the following points:

- The decision problem addressed in the MS was relevant to the NICE scope. However clinical advisors to the ERG differed in their opinion of whether bicalutamide represented a realistic comparator to degarelix.

- The included trials of degarelix were of good methodological quality and full clinical study reports for each trial were provided by the manufacturer.

1.6.2 Weaknesses and areas of uncertainty

With respect to the clinical effectiveness evidence the key areas of uncertainty identified by the ERG are as follows:

- The study duration of the included trials was too short to make meaningful conclusions about overall survival.

- It was incorrect to assume the efficacy and safety profiles of the LHRH agonist comparators are equivalent on the basis of one published paper and one poster that do not include all of the comparators.

- The MS does not explore the potential difference in overall survival for triptorelin in their analyses but instead claim that the results support the previous published paper and poster.

With respect to the MS *de novo* economic model, the key areas of uncertainty identified by the ERG are as follows:

- The model has a Markov treatment sequence structure which assumes an identical treatment sequence for all patients. As there is variation in the treatment sequence between patients this model structure is inappropriate. The ERG considers that a model structure that explicitly models time to metastatic disease and time to death would be more transparent, appropriate and flexible.
- LHRH agonists were considered equivalent in terms of efficacy and adverse events without adequate justification. The ERG believes that the efficacy and adverse events of each LHRH agonist should be modelled individually.
- Bicalutamide monotherapy was not included as a comparator within the MS.
- The analysis of the adverse event data was inappropriate. Firstly, the analysis should undertake a meta-analysis rather than simply pooling. Secondly, the analysis should compare the fit of additional parametric curves and the fit of the Weibull which was used in the MS was poor for some adverse events. The ERG was unable to address these issues as the individual patient data was not supplied.

The direction and magnitude of the bias caused by these issues is not clear.

The major issues with the data used to inform the MS *de novo* economic model are:

- The overall survival benefit associated with degarelix is associated with considerable uncertainty. The duration of the clinical trials was inappropriate to determine overall survival benefit. The data supporting the relationship between PSA progression and overall survival is inconclusive.
- The data on PSA progression and adverse events are for a maximum of one-year in duration so the manufacturer's model is based on extrapolation of these data which introduces considerable uncertainty.
- The frequency of flare protection was considerably lower in the trials than is normal in clinical practice in the UK.

1.7 Summary of additional work undertaken by the ERG

The MS searches were carried out in March 2013. The ERG updated the manufacturer's searches on 13th September 2013 with amended strategies to include drug subject headings and searched PubMed (8th October 2013) for electronic publications that were ahead of print and thus not indexed in Medline, Web of Science and Embase. A total of 1055 unique records were retrieved from the database searches. The ERG did not identify any additional relevant RCTs that were not already reported in the MS.

The ERG undertook a revised MTC using informative priors for the heterogeneity parameter and the baseline treatment effect, but non-informative priors for the treatment effects. The analyses showed that triptorelin was associated with lower mortality than leuprorelin (odds ratio 0.2753 95% CrI: 0.06429, 0.9731). The ERG undertook an additional analysis taking into account the different study durations between the trials. These results were also in line with the odds ratio results from the ERG's additional analysis.

The additional analyses undertaken by the ERG demonstrated the impact of several key assumptions on the ICER. The ERG base case analysis considered: 3-monthly triptorelin as a comparator; assumed LHRH agonists treatment was continued until death; assumed the hazard ratio for differential efficacy applied for one year; assumed the proportion of patients receiving chemotherapy after PSA progression was 70%; and the proportion of patients receiving abiraterone was 70%. The ERG base case was associated with an additional cost of £3,659 and a QALY gain of 0.25 and an ICER of £14,798 per QALY.

ERG scenario analyses demonstrated that this ICER was very sensitive to four model assumptions: (1) the exclusion of SCC adverse events from the analysis; (2) the modelling of fracture rates; (3) the assumption that PSA progression affects mortality rates in metastatic patients; and (4) the assumption of equal efficacy of degarelix and LHRH agonists. The ICER values obtained with these three assumptions were £25,486; £21,950; £17,067; and £35,589 respectively. Lastly an ERG scenario analysis which explored the possible benefits of degarelix for the subgroup 'patients with spinal metastases with actual or impending SCC' suggested that degarelix has the potential to be cost saving for this subgroup.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The MS describes the underlying health problem as 'advanced prostate cancer' (MS page 16), which encompasses locally advanced as well as metastatic prostate cancer. The description of the health problem focuses on the target condition, rather than prostate cancer more generally, and is grounded in the tumour, node, metastasis (TNM) classification of prostate cancer.[1] Locally advanced disease includes a spectrum of disease states including: extension of the disease through the prostate capsule (T3a disease); spread to the seminal vesicles (T3b disease); spread to adjacent structures, e.g. the bladder neck, external sphincter, rectum, levator muscles and pelvic wall (T4 disease);[2] and spread to the regional lymph nodes (N1 disease). Once metastases have developed distant from the prostate gland the health problem is described as metastatic disease (M1). The MS uses the terms "advanced prostate cancer" and "advanced hormone-dependent prostate cancer" interchangeably. Castration-refractory metastatic prostate cancer and localised prostate cancer were not considered. This is in accordance with NICE CG58,[2] which recommends medical or surgical castration for men with locally advanced or metastatic disease. Clinical advisors to the ERG considered the description of the underlying health problem to be appropriate and relevant to the decision problem.

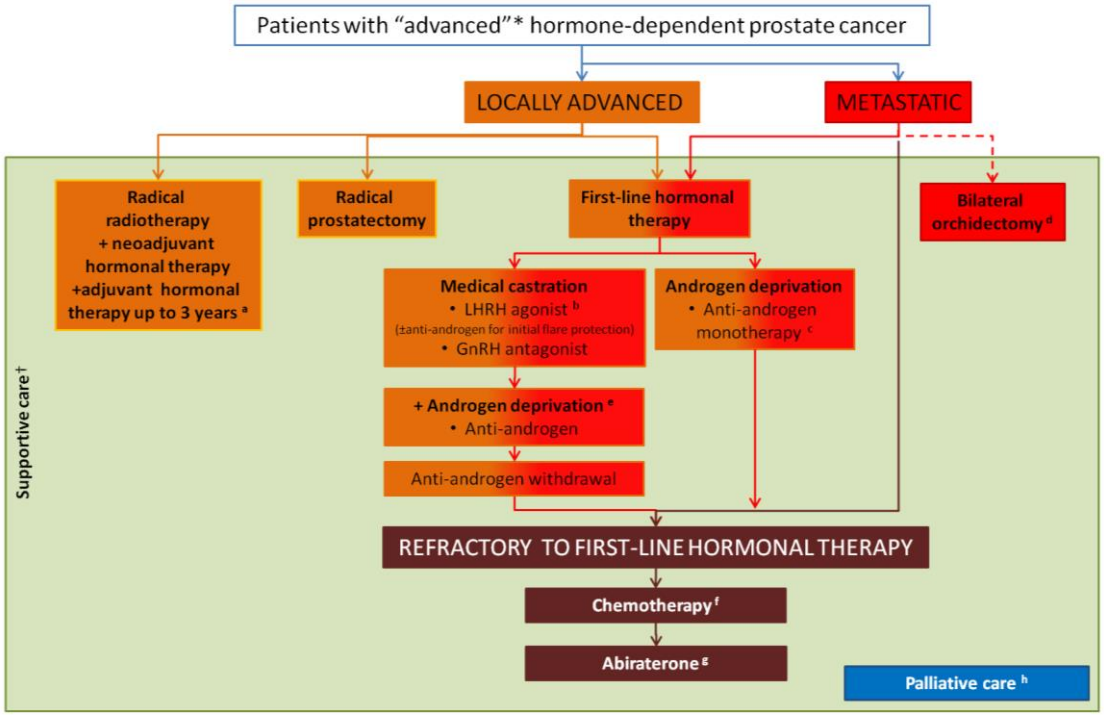
The incidence of prostate cancer estimated in the MS is based on independent data from the Office for National Statistics (ONS; 2008-2010)[3] and the British Association of Urological Surgeons (2011).[4] The manufacturer estimates the number of patients expected to be treated with hormonal therapy in England and Wales to be 15,458 in 2014, rising to 16,259 in 2018 (MS page 17). Drawing on data from Hospital Episode Statistics (HES), Radiotherapy dataset (RTDS), and Cancer Waiting Times Dataset (CWT),[5] these figures were calculated by multiplying prostate cancer incidence by incidence of patients treated with hormonal therapy without radiotherapy or prostatectomy (39%). An estimation of the number of patients with prostate-specific antigen (PSA) levels >20ng/ml is derived in the MS from the subgroup of patients from the main pivotal randomised controlled trial (RCT) of degarelix (CS21[6]) who had PSA levels >20ng/ml (48%). The manufacturer considers this subgroup to represent the indicated population with advanced hormone-dependent prostate cancer. This figure is then multiplied by the expected number of patients treated with hormonal therapy, which equates to 7,425 patients in 2014. Thus, the background estimates in the MS focus on a patient group in whom hormonal therapy is the only indicated treatment. However, the full patient populations in the included RCTs in the MS differed from this indication (see Sections 3 & 4 of this report). Overall mortality rates for prostate cancer are provided on page 18 of the MS.

These rates were estimated on the basis of ONS data,[3] and were stated to be 23.9% in England and 23.3% in Wales in 2008–10. The MS subsequently notes that much of the mortality associated with prostate cancer is attributable to men with hormone-refractory prostate cancer which is a more severe disease than the population under consideration in the MS.

2.2 Critique of manufacturer's overview of current service provision

The manufacturer presents a schematic of the current treatment pathway for advanced hormone-dependent prostate cancer which can be seen in Figure 1).

Figure 1. Current treatment pathway for advanced hormone-dependent prostate cancer replicated from page 20 of the MS



However clinical advice received by the ERG suggests that the diagram fails to accurately represent the clinical pathway in practice. The following issues are not adequately captured in the diagram:

i. The assumption is made that all patients failing androgen deprivation therapy will have chemotherapy. This is incorrect. Three clinical advisors to the ERG differed in their estimations of how many patients receive chemotherapy with the lowest estimate being 15% and the highest estimate being 70%.

ii. Patients undergoing radical local treatment with surgery or radiotherapy will fail in a proportion of cases. They will most likely subsequently receive hormone-based treatment at a later point in the pathway.

iii. The assumption is made that all patients will receive abiraterone. This drug has limited efficacy in poor performance patients (ECOG Performance Status 2 or higher).

iv. The sequencing of abiraterone after chemotherapy is inaccurate. This can (and is now often) given before chemotherapy as well as after. The diagram also omits the use of the competitive blocker, enzalutamide. Some patients will receive abiraterone and not chemotherapy.

v. The diagram implies that ADH blockade with GnRH analogues is discontinued after PSA failure. This is not accurate as treatment with hormone therapy normally continues until the end of life.

The ERG requested clarification from the manufacturer on the evidence supporting the validity of the clinical pathway in Figure 2. The manufacturer responded that they had consulted external clinical experts for further information to determine whether people continue on treatments through the pathway. *"This expert opinion indicates:*

1. Step 1 in treatment sequence:

Given that a patient fails (defined as 'experiences PSA progression') on treatment with LHRH agonists/antagonists the chance of them receiving anti-androgen addition for androgen deprivation (also known as complete androgen blockade) is >95%.

2. Step 2 in treatment sequence:

Given that a patient fails (defined as 'experiences PSA progression') on androgen deprivation, the chance of them moving to anti-androgen withdrawal is high (85%-100%), with most, if not all patients going through anti-androgen withdrawal.

3. Step 3 in treatment sequence:

Given that a patient fails (defined as 'experiences PSA progression') after anti-androgen withdrawal, the chance of them moving onto chemotherapy treatment with docetaxel or abiraterone is 50-70%, since many patients receive abiraterone via the Cancer Drugs Fund - however, docetaxel was placed before abiraterone in the clinical pathway presented in line with the reference case.

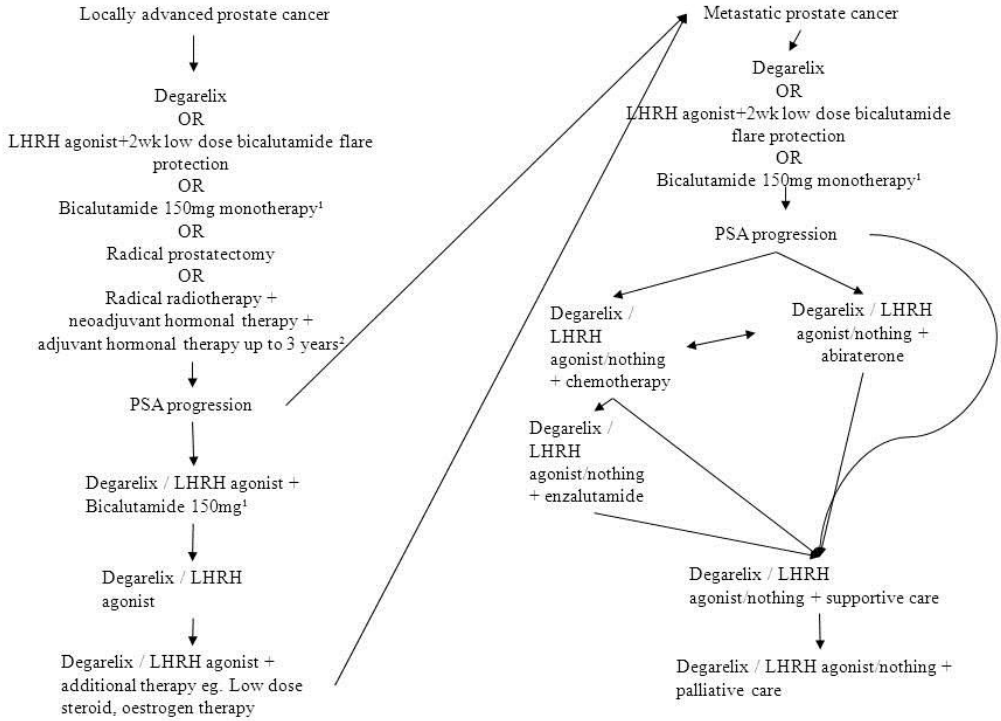
4. Step 4 in treatment sequence:

Of those patients that have been treated by docetaxel and failed, 70% will go on to receive abiraterone.

These percentages described above are largely in line with the assumptions made in the NICE STA model submitted, which provides sensitivity analysis results using these assumptions within the economic model.

The ERG propose the an alternative treatment pathway for patients in the decision problem to reflect clinical advise to the ERG.

Figure 2. Alternative current treatment pathway for advanced hormone-dependent prostate cancer proposed by the ERG



[1] Around 20-25% of patients will have a biochemical response with rising androgen levels. These patients will be withdrawn from anti-androgen therapy.
[2] Pelvic radiotherapy should also be considered for men with a >15% risk of pelvic lymph node involvement who are to receive this treatment

It should be noted that there may be delays in movement through the stages in the pathway following progression which occur in real life which are not reflected in the manufacturer's model.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

A summary of the decision problem (Table 1) as outlined in the final scope issued by NICE which was defined in the context of NICE Clinical Guideline No. 58 and addressed in the manufacturers' submission is presented in Table 1.

Table 1: Decision problem as outlined in the final scope issued by NICE and addressed in the manufacturers' submission (based on pages 30-32 of MS but amended by the ERG to reflect their opinion of the submission)

	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	Same as identified in the scope however the study population in the MS includes all stages of prostate cancer
Intervention	Degarelix	Same as identified in the scope
Comparators	• Gonadotrophin-releasing hormone agonists in combination with short-term anti-androgen treatment including: o Goserelin o Leuprorelin o Triptorelin • Bicalutamide	• Gonadotrophin-releasing hormone agonists including: o Goserelin o Leuprorelin o Triptorelin Bicalutamide was not included as a comparator in the base case. Short-term anti-androgen treatment was not used consistently in included evidence from the MS.
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.	• Overall survival • Progression-free survival • Testosterone response • Prostate-specific antigen (PSA) response • PSA progression-free survival • Adverse effects of treatment • Health-related quality of life.

	Final scope issued by NICE	Decision problem addressed in the submission
Economic analysis	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.	Cost-effectiveness of treatments will be expressed in terms of incremental cost per quality-adjusted life-year. The time-horizon of the cost-effectiveness analysis will be 20 years. Costs are considered from an NHS and Personal Social Services perspective.
Subgroups to be considered	If evidence allows, the following subgroups will be considered: • 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.	The subgroups considered include: • High-risk patients with PSA >20 ng/ml • Patients with pre-existing cardiovascular disease Only the first subgroup were considered in the economic analysis.
Special considerations, including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation.	N/A

3.1 Population

Degarelix is licensed in the UK for the treatment of advanced hormone-dependent prostate cancer.[7] The population described in the decision problem in the MS matches the population described in the final scope issued by NICE in accordance with NICE clinical guideline CG58.[2] However, the study population presented in the MS includes patients with all stages of prostate cancer, including localised and those with non-classifiable disease. The EU marketing authorisation restricts use of degarelix to patients with locally advanced and metastatic disease. Clinical advisors to the ERG suggest that due to the substantial proportion

of patients in the included trials that did not have advanced disease, the median baseline levels of prostate specific antigen (PSA) across the included trials are lower than what would be expected for those being offered hormone therapy in the UK.

Prostate cancer is described by the manufacturer to be the most common cancer in men, accounting for approximately 25% of new diagnoses of malignant cancer in men in England and Wales.[2] The condition is considered to be "advanced" by both the manufacturer and the NICE scope when the disease has become metastatic or locally advanced (M1 or N1 respectively according to classification on the Tumour Node Metastasis (TNM) clinical staging system.[1] NICE clinical guideline CG58[2] is currently under review and is due to be updated in January 2014. Presently, recommended treatment options for patients at the locally advanced stage include: first-line hormonal therapy; radical radiotherapy (with or without adjunctive hormonal therapy) or radical prostatectomy. Patients at the metastatic stage are offered hormonal therapy or bilateral orchidectomy. Hormonal therapy or androgen deprivation therapy (ADT) is offered as a medical approach to castration and generally comprises: i) luteinizing hormone-releasing hormone (LHRH) agonists (in combination with anti-androgen testosterone flare protection); ii) gonadotrophin releasing-hormone (GnRH) antagonists; and iii) anti-androgen monotherapy. These treatment options are the mainstay of patients with locally advanced prostate cancer until progression to hormone-refractory prostate cancer or end of life.

3.2 Intervention

Degarelix (Firmagon®) is a selective gonadotrophin releasing-hormone (GnRH) antagonist, which competitively and reversibly binds to pituitary GnRH receptors, leading to a rapid reduction in the release of the gonadotrophins luteinising hormone (LH) and follicle-stimulating hormone (FSH). A decrease in LH and FSH levels results in a rapid reduction of testosterone secretion by the testes to castrate levels.

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) granted marketing authorisation for degarelix in Europe, including the UK, on 17 February 2009.[7] Degarelix is the first GnRH antagonist to receive a licence for this indication in the UK. Degarelix was also accepted for use by the Scottish Medicines Consortium (SMC)[8] in 2011 and the All Wales Medicines Strategy Group (AWMSG)[9] in 2012. Degarelix has received regulatory approval in 64 countries in addition to the UK (MS page 12).

Administration of degarelix is by subcutaneous injection in the abdomen. The licensed dose is one starting dose of 240 mg (two injections of 120 mg each), followed, after one month, by maintenance doses of 80 mg administered every 28 days. Degarelix is available as a powder and solvent for solution for injection in vials containing 120 mg or 80 mg degarelix (as acetate). The manufacturer describes (MS page 6) that patients receive one single continuous course of treatment with degarelix until the disease progresses to hormone-refractory prostate cancer, or until the end of life (depending on local practice).

3.3 Comparators

The NICE scope stated the comparators to degarelix include:

- LHRH agonists (in combination with short-term anti-androgen treatment): goserelin; leuprorelin; and triptorelin
- Bicalutamide

The MS includes the comparators: goserelin; leuprorelin; and triptorelin, but disputes the inclusion of bicalutamide monotherapy as a comparator. The manufacturer argues that bicalutamide monotherapy is licensed for use only in locally advanced disease and not for metastatic disease, unlike degarelix (MS page 22). The manufacturer also states that *"published, randomised controlled trial (RCT) evidence comparing bicalutamide monotherapy with degarelix and/or LHRH agonists is lacking. It was, therefore, not possible to complete a robust mixed treatment comparison to compare degarelix with bicalutamide monotherapy."* Input from clinical advisors to the ERG stated that bicalutamide monotherapy, whilst possessing a different mechanism of action to the GnRH agonists/antagonists, represents a treatment option for a proportion of patients relevant to this decision problem. Furthermore, bicalutamide monotherapy may be a preferred treatment option in some patients, particularly those with locally advanced disease and for younger patients in whom maintenance of sexual function is a preferable.

The ERG considers that whilst degarelix may not be directly comparable to bicalutamide in the clinical endpoints related to testosterone response, there are head-to-head comparisons of bicalutamide and LHRH agonists[10,11] with data relevant to quality of life which may be of relevance to this appraisal. The manufacturer states that *"degarelix will keep patients on first-line hormonal therapy for longer, which is more cost-effective and associated with better health-related quality of life than subsequent treatment stages"* (MS page 27). Such a claim has not been substantiated using the available evidence presented by the manufacturer. The ERG believes that it may have been possible to make naïve indirect comparisons of

bicalutamide versus degarelix for certain outcomes using data for the locally advanced subgroups within the degarelix trials. It is the opinion of the ERG that bicalutamide can be considered as an appropriate comparator to degarelix in the locally advanced subgroup only and the fact that this does not reflect the entire target population does not justify its exclusion from the decision problem. Two clinical advisors to the ERG have stated that bicalutamide monotherapy does represent a treatment option for a proportion of people in the target population whilst one clinical advisor considered that bicalutamide monotherapy is used rarely in clinical practice. The ERG does however recognise that few data are available on the usage of bicalutamide monotherapy in the target population in the UK. Moreover, estimates of current bicalutamide monotherapy usage are not provided in the MS.

The NICE scope specifies that the comparator LHRH agonists should be used in combination with short-term anti-androgen treatment. Short-term anti-androgen treatment with non-steroidal anti-androgen drugs (such as bicalutamide or cyproterone acetate) is used to prevent testosterone flare associated in the early stages of treatment with LHRH agonists. The RCTs of degarelix versus leuprorelin or degarelix versus goserelin included in the MS did not consistently use anti-androgen flare protection for the LHRH comparator arms. The rates of bicalutamide flare protection were 11% in trials CS21 and 13.5% in CS35. 100% of patients in the comparator arm of CS28; CS30 and CS31 were reported to receive bicalutamide flare protection but flare protection was not reported for trial CS37. Clinical advisors to the ERG have stated that close to 100% of patients receiving LHRH agonists will receive anti-androgen flare protection in UK clinical practice.

The manufacturer selects goserelin as the comparator to degarelix for the base case on the basis that: i) goserelin is the most frequently used LHRH agonist in the UK (MS page 23); and ii) the LHRH agonists are equally efficacious and safe. However, the large pivotal trial for degarelix (CS21) presented in the MS evaluated degarelix versus leuprorelin. This is also the trial which provides the evidence for the PSA> 20 ng/ml subgroup within the manufacturer's economic analysis.

Clinical advisors to the ERG suggested that surgical castration could be considered as an appropriate comparator to the decision problem. However as the population in the NICE scope is patients in whom orchidectomy is not preferred the manufacturer is justified in not including surgical castration in the decision problem.

3.4 Outcomes

The relevant outcomes from the NICE scope are considered in different analyses throughout the MS. Table 2 summarises the manufacturer's exploration of clinical efficacy through the various outcomes from either:

- narrative from the 6 individual trials of degarelix which were conducted by Ferring (CS21; CS28; CS30; CS31; CS35; CS37);
- pooled analyses from different combinations of the 6 trials of degarelix;
- meta-analyses from the 6 trials of degarelix;
- a mixed treatment comparison (MTC) with comparator drugs from published studies.

Table 2. Table of outcomes specified in the NICE scope as included in the assessment of clinical effectiveness in the MS

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	page 71		page 78/79	page 86-88
Progression free survival [a]	page 71 appendix B			
Testosterone response [b]	page 64	page 74		
PSA response	pages 69/71	page 70 [e]	page 76/77	
Time to PSA progression				
PSA progression-free survival [d]	page 67-69	page 70/71 [f]		
Adverse events of treatment		page 95/96	page 93-95	
Health-related quality of life	page 72/73			
Prostate volume [c]	page 65/66		page 75	
International prostate symptom score (IPSS)	page 66/67		page 75/76	
Serum alkaline phosphatase (s-ALP)	page 72	page 72		

[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 [12]

Although overall survival would be considered as the most relevant final outcome, the trials reported in the MS for demonstration of clinical effectiveness of degarelix are between 3 to 12 months in duration only. The trials do not include sufficient follow-up to provide reliable estimates of survival between the competing treatment options. As reported in the MS (page 18), one-year overall survival rates are 92.6% for patients with prostate cancer according the

Office for National Statistics. In accordance with this, the rates of events for mortality in the included trials are low (see Section 4 of this report). Moreover, expert clinical advice received by the ERG suggests that comparative data relating to one-year survival should be treated with caution as trials of this size and duration are not sufficient to capture meaningful differences in survival in this stage of disease and that at least 5 year follow-up would be required to gather appropriate numbers of events (deaths).

The response rate outcomes used in the MS can be considered as surrogate outcomes which are focused on biochemical endpoints, as opposed to clinical endpoints such as tumour volume. The ERG requested clarification of the manufacturer's definition of "response rate" considering that both PSA response and testosterone response are considered in the MS. The manufacturer responded that "*response is defined as the absence of PSA recurrence. In CS21 and CS21A PSA recurrence is defined as an increase in PSA of ≥50% from nadir and a PSA reading of ≥5 ng/ml.*"

3.5 Other relevant factors

Subgroups which were identified as relevant in the NICE scope but not examined in the MS were:

- 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.

The MS states *"The subgroups to be considered are those for which a sufficiently large number of patients was included in randomised clinical trials and sufficient data have been generated to provide a robust analysis"* (page 32). The ERG requested clarification from the manufacturer on the exclusion of key subgroups from the NICE scope and for clarification over the "sufficiently large" number of patients needed to generate a robust analysis. The manufacturer responded that:

"Patients with high tumour volume with impending or actual urinary outflow obstruction were studied in the CS28 clinical trial (n=42). Data on prostate or tumour volume have not been recorded systematically in any other trials (since TNM staging for the indication was collected). This means that patients with high tumour volume could not be identified outside

of CS28. Data were not collected on whether or not patients were contraindicated to anti-androgen treatment. Patients at risk of evolving cardiovascular co-morbidity could not be considered as a subgroup since prospective measurements or evaluations were not assessed during the trials."

The manufacturer does consider two subgroups from *post hoc* analyses. The first is patients with PSA >20 ng/ml from trial CS21, and the second is a pooled analysis from the six included trials of degarelix in patients with pre-existing cardiovascular disease. The ERG requested clarification from the manufacturer on how the *post-hoc* pre-existing cardiovascular disease subgroup was defined. The manufacturer responded that the 5 following Standardised MedDRA Queries (SMQs) applied to individual patient medical records:

- Myocardial infarction (SMQ)
- Ischaemic cerebrovascular conditions (SMQ)
- Haemorrhagic cerebrovascular conditions (SMQ)
- Embolic and thrombotic events, arterial (SMQ)
- Other ischaemic heart disease (SMQ)

Clinical advisors to the ERG highlighted that there is increasing focus on the correlative relationship between androgen deprivation therapy and cardiovascular mortality and morbidity.[13,14] Therefore whilst the patient subgroup of pre-existing cardiovascular risk is therefore considered to be highly relevant to this appraisal, clinical advice to the ERG was that there is currently a lack of prospectively designed trials which could adequately examine this relationship.

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods used by the manufacturer to systematically review clinical effectiveness evidence

The manufacturer undertook two systematic reviews to evaluate the clinical evidence for the treatment of advanced hormone-dependent prostate cancer. The objective of the first systematic review was to identify the relevant clinical evidence available for degarelix in the target population (MS page 34). The objective of the second systematic review was to identify clinical evidence for the comparators to inform the mixed treatment comparison (MTC) and is discussed in section 4.3 of this report. The inclusion criteria for the review population; intervention; comparators and outcomes are in line with the NICE scope for this appraisal.

One search was conducted to produce evidence to inform both the review of clinical effectiveness evidence for degarelix and the review to identify evidence for the MTC of degarelix versus the comparators: leuprorelin; goserelin; and triptorelin in (Section 6.7; MS page 81).

The manufacturer reported searching four databases: Medline; Embase; Cochrane Library; and Web of Science. However, only one search strategy was provided in an appendix to the MS. The ERG acknowledge receipt of the full Medline and Embase, Cochrane Library and Web of Science strategies following requests made during the clarification process for this appraisal. However, prior to receiving the strategies, the ERG attempted to replicate the MS search strategy (page 232 of the MS) and translated the search across the other databases. The translated search strategies by the ERG can be found in Appendix 2 of the ERG report.

The free-text terms for both intervention and comparators were considered comprehensive. However, the MS strategy lacked the appropriate field tags (.mp.) to show that subject headings in Medline and Embase were searched for both the drug and comparators. In the manufacturer's clarification response, only degarelix and prostate cancer terms were mapped to the appropriate subject headings in Medline and Embase. The ERG identified two problems. Firstly, mapping of these terms were omitted from the Cochrane Library search. Secondly, mapping for the comparators and hormone antagonists were omitted from all three databases (see ERG strategies in Appendix 3 for examples). The absence of these terms could reduce the sensitivity of the search. However, due to time restrictions the ERG could not confirm if studies for indirect comparison have been missed.

The conceptual group of search terms in the strategy is coherent but was not consistently applied in the translation of the search across the databases. In the MS search strategy, terms for degarelix were combined with terms for prostate cancer. Since degarelix is not indicated in any other condition, the sensitivity of the search could be increased by searching for the intervention alone in the absence of prostate cancer terms. This was shown to be the case in the manufacturer's provided Cochrane Library strategy (Clarification letter, Cochrane strategy).

The manufacturer reported using SIGN filters for retrieving RCTs, systematic reviews and meta-analysis studies. However, the filters applied in the Medline and Embase strategies were not those of SIGN filters (http://www.sign.ac.uk/methodology/filters.html). The translation of the search filter in the Web of Science was considered too restrictive. In addition, a document type limit (by conference proceedings and meeting abstracts) was applied by the manufacturer in the Web of Science search. The ERG considers that this limit was unnecessary because of the nature of the database that was searched in the Web of Science which was a "Conference Proceedings Citation Index" and "Science and the Conference Proceedings Index - Social Science and Humanities". This additional limit is likely to have reduced the sensitivity of the search.

The MS searches were carried out in March 2013. The ERG updated the search on 13th September 2013 with the amended strategies by the inclusion of drug subject headings and the number of records retrieved are summarised in Appendix 2. In addition, the ERG searched in PubMed (8th October 2013) for electronic publications that were ahead of print and thus not indexed in Medline, Web of Science and Embase. A total of 1055 unique records were retrieved from the database searches. Several ongoing studies that were identified and reported as not yet published in the MS were retrieved in the updated ERG search. The ERG did not identify any additional relevant RCTs that were not included in the MS.

4.1.2 Inclusion/exclusion criteria used in the systematic review for clinical effectiveness

The inclusion and exclusion criteria applied in the systematic review conducted by the manufacturer are presented in Table 3. The MS states that all records were examined by two independent reviewers, and that any disagreements were resolved by discussion (MS page 35).

Table 3. Inclusion criteria used for study selection as indicated in the MS (Table 8; page 36)

Inclusion criteria	
Population	Adult male patients with advanced hormone-dependent prostate cancer*
Interventions	Degarelix
Comparators	Luteinising hormone-releasing hormone agonists • Goserelin • Leuprorelin • Triptorelin Bicalutamide monotherapy
Outcomes	• Overall survival • Progression-free survival • Response rate • Testosterone response • PSA response (PSA percentage change from baseline and PSA progression [recurrence or failure]) • PSA PFS • Time to PSA progression • Adverse effects of treatment • Health-related quality of life
Study design	Randomised controlled trials and non-randomised clinical trials
Language restrictions	No language restrictions
Exclusion criteria	
Population	Not further specified
Interventions	Not further specified
Comparators	Not further specified
Outcomes	Not further specified
Study design	Phase I pharmacokinetic studies
Language restrictions	N/A

Key: N/A = not applicable; PSA = prostate-specific antigen; PFS = progression-free survival
* Available clinical trials of degarelix usually included patients with prostate cancer of all stages, so studies of patients with all stages of prostate cancer suitable for treatment with hormonal therapy were included.

The ERG notes 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 the available trials included patients at all stages of disease that were suitable for hormone therapy. Clinical advisors to the ERG suggested that inclusion of patients in the earlier stages of prostate cancer is unlikely to bias the results of the assessment to degarelix or LHRH agonists providing that the severity of disease is comparable between intervention and comparator groups. However, it is possible that fewer adverse events may be observed in these less advanced patients. The inclusion criteria for this systematic review are considered appropriate.

4.1.3 Study selection in the clinical effectiveness review

Six multicentre, open-label RCTs of degarelix were included in the clinical effectiveness review (MS page 37). Details of the six degarelix trials are presented in Table 4. Clinical study reports (CSR) for all six trials were provided to the ERG by the manufacturer.

Table 4. Intervention and comparator groups in the included studies

Trial	Intervention	Randomised	Comparator	Randomised	Duration
CS21 Klotz *etal*, 2008[15]	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 [16]	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 [17]	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[18] 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

Four trials used the licensed degarelix initial dose of 240 mg followed by monthly maintenance doses of 80mg. However, CS35 used an unlicensed three-monthly 480mg dose. This limits the applicability of CS35 to the decision problem. Trial CS37 included both an intermittent (6 maintenance doses of 80mg during days 28 to 168) and a continuous (13 maintenance doses of 80mg during days 28 to 168) regime of degarelix in separate trial arms. CS21 included a second monthly degarelix treatment arm (240mg followed by 160mg/ month) as well as the licensed doing regimen. The dosing regimens across the six included RCTs are summarised in Table 5. The comparator LHRH agonists were leuprorelin (CS21 and CS37) and goserelin (CS28; CS30; CS31; CS35). No head-to-head trials of degarelix versus either triptorelin or bicalutamide were identified. One limitation of the trials with respect to the decision problem was the low use of bicalutamide flare protection in two trials: CS21 and CS35 for the LHRH comparators. In these trials, 11% and 13.5% of patients, respectively, received flare protection. However, clinical opinion suggests that the use of bicalutamide or cyproterone acetate for flare protection would be provided for most prostate cancer patients in the UK.

With the exception of CS37, which was conducted solely in the USA, all trials involved an international base, with four trials including UK centres (CS 21, CS28, CS30, and CS35). Treatment duration ranged from three months (CS28, CS30, CS31) to 14 months (CS37). All trials except CS37 included an extension phase.

All trials (CS21; CS28; CS30; CS31; CS35; CS37) included patients with histologically confirmed prostate cancer. A summary of inclusion and exclusion criteria for each of the six RCTS is shown in Table 5.

Table 5. Summary Table of inclusion and exclusion criteria for the included trials

Inclusion	Exclusion
CS21	
Histologically confirmed andenocarcinoma of the prostate (all stages), indicated for androgen treatment Male patients aged ≥18 years Serum testosterone >1.5 ng/mL at Screening ECOG score ≤2 PSA ≥2 ng/mL at Screening Life expectancy of at least 12 months	Previous or concurrent hormonal management of prostate cancer Concurrent treatment with a 5-α reductase inhibitor Candidate for radical prostatectomy/ radiotherapy At risk of, or pre-existing, Torsades de Pointes ventricular arrhythmia Cancer within last five years Had a known or suspected hepatic, symptomatic biliary disease Any clinically significant laboratory abnormalities that may interfere with treatment
CS28	
Aged ≥ 18 years Histologically confirmed prostate cancer (Gleason graded, all stages) in which endocrine treatment was indicated. PSA level at screening >10 ng/mL. IPSS ≥12. ECOG score of ≤2. Estimated life expectancy at least 12 months. The prostate size was >30 cubic centimetres (cc), measured by TRUS. For patients who had received hormonal prostate cancer treatment: demonstrated response to the previous hormonal prostate cancer treatment.	Any previous treatments for prostate cancer except for hormonal treatment that was to have been terminated at least six months before screening. Previous trans-urethral resection of the prostate. Was currently treated with the 5-alpha reductase inhibitors finasteride or dutasteride, or with α-adrenoceptor antagonists. Patients who required external beam radiotherapy to be started at the same time as hormone therapy. At risk of, or pre-existing, Torsades de Pointes ventricular arrhythmia History / presence of another cancer within 5 years Any other clinically significant disorder that could affect the results
CS30	
Aged ≥ 18 years Planned to undergo radical radiotherapy treatment and in whom neoadjuvant endocrine treatment was indicated Tumour, Nodule, and Metastatic (TNM) stage T2 (b or c)/T3/T4, N0, M0; or Gleason score ≥7 or PSA ≥10 ng/mL ECOG score of ≤2 Estimated life expectancy at least 30 months Prostate size >30 cubic centimetres, measured by TRUS	Any previous treatment for prostate cancer Previous transurethral resection of the prostate Patients who were lymph node positive or had other metastatic disease Was not considered a candidate for hormonal therapy as neoadjuvant treatment to radiotherapy Currently treated with 5-α reductase inhibitor or α-adrenoceptor antagonist Previous history or presence of another malignancy At risk of, or pre-existing, Torsades de Pointes ventricular arrhythmia Any other clinically significant disorder that could affect the results
CS31	
Aged ≥ 18 years Histologically confirmed prostate cancer (Gleason graded, all stages) in which	Any previous treatments for prostate cancer including trans-urethral resection of the prostate Not a candidate for medical castration

Inclusion	Exclusion
endocrine treatment was indicated. PSA ≥2 ng/mL at Screening Prostate size >30 cubic centimetres, measured by TRUS Patient had a bone-scan within 12 weeks before inclusion Patient had to be able to undergo transrectal examinations Estimated life expectancy > 12 months	Currently treated with 5-α reductase inhibitor or α-adrenoceptor antagonist Required radiotherapy during the trial History or presence of another malignancy Any other clinically significant disorder that could affect the results At risk of, or pre-existing, Torsades de Pointes ventricular arrhythmia
CS35	
Histologically confirmed adenocarcinoma of the prostate for which endocrine treatment (except for neoadjuvant hormonal therapy) was indicated. Had a PSA level meeting one of these criteria: For treatment-naïve patients: screening PSA level of ≥2 ng/mL. For patients with recurrence after radical prostatectomy: PSA increase of ≥0.2 ng/mL from the previous test on two consecutive measurements. For patients with recurrence after radiotherapy or cryotherapy: PSA (two measurements) >2 ng/mL higher than a previously confirmed PSA nadir. Age ≥ 18 years Baseline testosterone ≥1.5 ng.Ml ECOG score ≤2 Life expectancy ≥ 12 months	Previus or current hormonal management of prostate cancer Treatment with 5-α reductase inhibitors prior to screening Candidate for curative therapy In need of neoadjuvant hormone therapy At risk of, or pre-existing, Torsades de Pointes ventricular arrhythmia History or presence of another malignancy Clinically significant laboratory abnormalities that may interfere with trial results Any other clinically significant disorder that could affect the results Incomplete recovery from any major surgery
CS37	
Had rising PSA* after having undergone primary therapy for localized prostatic carcinoma and the investigator assessed that androgen deprivation therapy was warranted. Histologically confirmed (Gleason graded) adenocarcinoma of the prostate (nonmetastatic). Screening testosterone ≥1.5 ng/Ml Aged ≥ 18 years ECOG score ≤2 Life expectancy ≥ 15 months	Hormone therapy within 6 months of randomisation; >4 months' neoadjuvant hormone therapy at any time in patient's history; >6 months adjuvant therapy at any time in patient's history Subjects being treated with 5-alpha reductase inhibitors at the time of enrolment must have remained on a stable dose throughout the trial. History or presence of another malignancy Clinically significant laboratory abnormalities that may interfere with trial results Any other clinically significant disorder that could affect the results Had received ketoconazole or diflucan in the last 28 days preceding the Screening Visit

4.1.4 Data extraction and quality assessment

The MS states that data were extracted from clinical study reports and end-of-trial tables, as well as published RCT reports and conference abstracts (page 39). Inclusion of clinical study reports is likely to provide more comprehensive results and to minimise the possibility for bias through selective reporting.[19] In addition, data extraction results were provided in the appendices to the MS. However, the manufacturer did not indicate whether the data extraction was validated by double-checking and consensus discussion with more than one reviewer.

The MS provides a narrative summary of quality assessment (pages 61-62), and includes a table which provides an overview of the quality assessment results in Appendix B (Table B8). However, there was no indication whether the quality assessment was validated by independent scoring and consensus discussion with more than one reviewer. The criteria used by the authors were standard, appropriate, and are coherent with the criteria for risk of bias assessment required from a STA.

The quality of the included trials was generally acceptable, with the two main potential sources of bias being lack of blinding and allocation concealment. As the MS notes, blinding of participants and care providers was impossible due to the different methods of administration for degarelix and LHRH agonists. Some information on outcome assessor blinding was also provided in Table B8 in Appendix B of the MS: only trial CS21 blinded outcome assessment. Lack of blinding for participants, care professionals, and outcome assessors, therefore represents the most significant source of bias among the studies. In addition, no studies provided sufficient information to confirm whether allocation concealment was adequately performed.

4.1.5 Degarelix trials omitted from the clinical effectiveness review

The ERG asked the manufacturer to clarify the omission of 12 completed clinical trial records of studies on degarelix conducted by the manufacturer that were not included in the MS. These twelve studies of degarelix in patients with prostate cancer were identified from clinicaltrials.gov. The manufacturer provided reasons for omission for eight single arm trials of degarelix in Table 6.

Table 6. Eight trials identified by the ERG with reasons provided by the manufacturer for omission from the MS from the clarifications process

Trial details	Reason provided by manufacturer for omission
NCT00117949 (CS06)	
Study Investigating the Pharmacokinetics, Pharmacodynamics and Safety of FE200486 (Completed 2004; Has results) Enrolment= 82	Pharmacokinetics and pharmacodynamics design. Single dosing regimen (40-160 mg) of degarelix was not relevant.
NCT00117312 (CS06A)	
Extension Study Investigating the Long-Term Safety and Tolerability of Repeat Doses of FE200486 in Prostate Cancer Patients (Terminated 2005; Has results) Enrolment= 37	Early safety and tolerability investigation. Only 37 of the 82 patients in CS06 were included
NCT00818623 (CS07)	
Investigation of a New Trial Drug (FE200486) in Prostate Cancer Patients (Completed 2004; Has results) Enrolment= 172	A single dose study investigating the pharmacokinetics, pharmacodynamics and safety of degarelix
NCT00245466 (CS02A)	
Study Investigating the Long-Term Safety and Tolerability of Repeated Doses of Degarelix in Prostate Cancer Patients (Terminated 2006; Has results) Enrolment= 88	In CS02, the loading dose regimen was no longer relevant. Only 88 of the 129 patients in CS02 were included in CS02A
NCT00215657 (CS07A)	
Extension Study Investigating the Long-Term Safety and Tolerability of Repeat Doses of FE200486 in Prostate Cancer Patients (Terminated 2006 Has Results) Enrolment= 131	CS07 was a trial for ascending single doses. Only 131 of the 172 patients were recruited in CS07A
NCT00117286 (CS14A)	
Extension Study Investigating the Long-Term Safety of Degarelix One-Month Depots in Patients With Prostate Cancer (Completed 2009; Has results) Enrolment= 57	All patients receive 160mg maintenance dose, which is not relevant in terms of licensed dose regimen (240/80 mg)
NCT01071915 (CS42)	
Efficacy and Safety of Degarelix One Month Dosing Regimen in Korean Patients With Prostate Cancer (Completed 2011; Has results) Enrolment= 157	The results for CS42 were reported in CS42A, which was referred to within the submission.
NCT00738673 (CS27)	
Degarelix as Second-Line Hormonal Treatment After Prostate-specific Antigen (PSA)-Failure in GnRH Agonist Treated Patients With Prostate Cancer (Completed 2011; Has results) Enrolment = 37	An exploratory study of second-line degarelix treatment after PSA-failure in GnRH agonist treated patients

The ERG considers the reasons for omitting trials: NCT00117949; NCT00117312; NCT00818623; NCT00245466; NCT00215657; NCT00117286; NCT01071915; and NCT00738673 from the clinical review of degarelix and from the MTC to be sufficient as they were single arm trials. However, these trials should have been included in Section 6.8

"*Non-RCT evidence*" in which the manufacturer describes evidence from dose-finding trials. These eight trials are all phase II or III trials and therefore do not fit the manufacturer's exclusion criteria of "*phase I pharmacokinetic studies*" (MS page 36).

Four further completed trials of degarelix were referred to by the manufacturer as "*No results available yet*" (see Table 7). These studies are also single arm trials of degarelix and the ERG considers that the results of these trials, if available, would also be relevant to the non-RCT evidence base for degarelix.

Table 7. Four trials identified by the ERG stated by the manufacturer to have "*no results available yet*" from the clarifications process.

Clinical trial no.	Trial details	Reason provided by manufacturer for omission
NCT01220869 CS43	A Study of Degarelix in Taiwanese Patients With Prostate Cancer (Completed 2012; No results available) Enrolment = 110	No results available yet.
NCT00801242 CS29	Intermittent Treatment With Degarelix of Patients Suffering From Prostate Cancer (Completed 2013; No results available) Enrolment = 220	No results available yet.
NCT01491971	Intramuscular Injections of Degarelix Administered in 1-Month Dosing Regimens in Patients With Prostate Cancer (Completed 2012; No results available) Enrolment = 76	No results available yet.
NCT01344564	Initiation of Androgen Deprivation Therapy for Prostate Cancer Using Degarelix Followed by Leuprolide (Completed 2012; No results available) Enrolment = 50	No results available yet.

Selective use of trials for pooled analyses/ meta-analyses in the MS

The MS states that all identified RCTs of degarelix versus an LHRH agonist (with or without flare protection), or bicalutamide monotherapy, were included in the review (MS page 44). The data from all six trials were reviewed and discussed in the narrative synthesis of findings. However, the manufacturer combines the trials in different combinations to produce *post* hoc pooled analyses. Certain trials were excluded from subsequent pooled analyses across various outcomes:

- *Cumulative probability of testosterone levels ≤0.5 ng/ml*

Two trials (CS35 and CS37) were excluded from the pooled analysis of this endpoint. CS37 did not measure this outcome and CS35 did not use the UK licensed dose of degarelix. Clinical advice received by the ERG suggests that the exclusion of CS35 and CS37 on these grounds was appropriate.

- *Reduction in prostate size*

Three trials were excluded from this analysis (CS21, CS35, and CS37). Since none of these trials included data on this outcome, these exclusions were considered appropriate.

- *IPSS scores*

Three trials were excluded from this analysis (CS21, CS35, and CS37). Of these trials, only CS35 evaluated IPSS scores. As this trial did not use the licensed dose, exclusion was considered appropriate.

- *PSA response*

CS35 and CS37 were excluded on the grounds that they did not use the UK licensed dosing regimens. Their exclusion from the analysis was considered appropriate.

- *Overall survival*

Survival data from CS37 were excluded from the meta-analysis because *"the degarelix monthly maintenance dose may not be compatible with the leuprorelin three-month regimen"* (MS page 78). However, survival data from another 3-month maintenance trial, CS35, were included in this analysis. The inclusion of this trial seems inconsistent with the meta-analyses of other outcomes, and was not justified in the MS. The ERG requested justification from the manufacturer for the inclusion of trial CS35 in the analysis for the *post* hoc PSA subgroup analysis and overall survival after stating that the this trial was not *"fully applicable to the decision problem due to the use of an unlicensed dose of degarelix"* (MS page 65) which has an intermittent dose of degarelix versus an intermittent dose of goserelin. Conversely the manufacturer excludes trial CS37 which has both continuous and intermittent phases of degarelix versus intermittent leuprorelin. The manufacturer responded that *"CS35 and CS21 (the pivotal phase III trial) share a similar trial design and patient inclusion criteria, therefore the patient baseline characteristics for these trials are reasonably comparable, warranting data to be pooled. Conversely, the CS37 trial was designed to evaluate intermittent versus continuous therapy, and the patient inclusion criteria were different to the other five RCTs, thus excluded from the meta-analyses."* The ERG considers that similar inclusion criteria does not warrant data to be pooled when the intervention dosage regimens are discrepant and that trial CS35 should have been excluded from these analyses.

4.2 Summary and critique of submitted clinical effectiveness evidence for the intervention

4.2.1 Summary and critique of submitted clinical evidence for degarelix trials included in the clinical effectiveness review

The baseline characteristics of the patients in each trial are shown in Table 8. The numbers in each group are based on the full analysis set (FAS) population. The MS stated that no statistically significant differences between treatment groups were seen in baseline characteristics (MS page 61), however p-values for between-group comparisons were not provided. The percentage of patients with locally advanced or metastatic prostate cancer varied from 5.5% in CS37, to 49% in CS21. Age and baseline testosterone levels were comparable across the trials, where reported, while a range of PSA levels were seen both within and between trials. As stated in Chapter 3, clinical advice to the ERG was that the median baseline PSA levels of all trials, except for trial CS28, are somewhat lower than what would be expected in clinical practice. These lower PSA levels are likely to be due to the wider inclusion criteria and subsequently lower severity of disease in the trial populations than the target population.

Table 8. Baseline participant characteristics from the 6 included RCTs replicated from Appendix B of the MS

	Treatment group		
Trial CS21	**Degarelix 240/160mg (n=202)**	**Degarelix 240/80mg (n=207)**	**Leuprorelin 7.5mg (n=201)**
Median (range) age (years)	72 (50-88)	72 (51-89)	74 (52-98)
Median testosterone ng/ml (IQR)	3.78 (2.86, 5.05)	4.11(3.05,5.32)	3.84(2.91,5.01)
Median PSA ng/ml (IQR)	19.9 (8.2, 68)	19.8 (9.4, 46)	17.4 (8.4, 56)
Prostate cancer stage n (%):			
Localised	59 (29)	69 (33)	63 (31)
Locally advanced	62 (31)	64 (31)	52 (26)
Metastatic	41 (20)	37 (18)	47 (23)
Not classifiable	40 (20)	37 (18)	39 (19)
Gleason grade n (%)			
2-4	21 (11)	20 (10)	24 (12)
5-6	67 (34)	68 (33)	63 (32)
7	56 (28)	63 (30)	62 (31)
8-10	56 (28)	56 (27)	51 (26)
Trial CS28	**Degarelix (n=27)**		**Goserelin (n=13)**
Median (range) age (years)	68 (53, 87)		72 (57, 85)
Median testosterone ng/ml (range)	4.2 (1.1, 6.7)		3.9 (2.7, 7.4)
Median PSA ng/ml (range)	54.8 (8, 1914)		41.1 (14.6, 348)
Prostate cancer stage n (%)			
Localised	4 (15)		0 (0)
Locally advanced	4 (15)		1 (8)
Metastatic	10 (37)		4 (31)
Not classifiable	9 (33)		8 (62)
Gleason score n (%)			
5-6	2 (7)		0 (0)
7-10	25 (93)		13 (100)
Mean (SE) IPSS total score	20.1 (1.1)		21.1 (1.6)
Mean (SE) IPSS QoL score	3.6 (0.3)		3.2 (0.5)
Mean (SE) prostate volume (ml)	53.5 (5.5		50.3 (4.5)
Trial CS30	**Degarelix (n=180)**		**Goserelin (n=64)**
Mean (SD) age (years)	70.6 (6.37)		70.8 (5.96)
Mean (SD) testosterone ng/ml	4.18 (1.72)		4.45 (1.49)
Median (range) testosterone ng/ml	3.92 (0.58, 11.2)		4.42 (0.19, 8.16)
Mean (SD) PSA ng/ml	17.4 (30.1)		13.4 (12.9)
Median (range) PSA ng/ml	10.0 (2.5, 339)		9.75 (2.9, 80)
Prostate cancer stage n (%)			
Localised	111 (62)		41 (64)
Locally advance	63 (35)		20 (31)
Not classifiable	6 (3)		3 (5)
Gleason score n (%)			
2-6	41 (23)		12 (19)
7	97 (54)		42 (66)
8-10	42 (23)		10 (16)
Mean (SD) IPSS total score	9.5 (6.71)		8.5 (6.3)
Mean (SD) IPSS QoL score	2.27 (1.63)		1.94 (1.56)
Mean (SD) total prostate volume ml	50.9 (20.3)		52.5 (18.8)
Median (range) days since prostate cancer diagnosis	75 (14, 1378)		72 (17, 1526)
Trial CS31	**Degarelix (n=82)**		**Goserelin (n=97)**

	Treatment group		
Mean (SD) age (years)	71.9 (7.71)		73 (7.1)
Mean (SD) testosteroine ng/ml	4.25 (1.88)		4.43 (1.64)
Median (range) testosterone ng/ml	4.08 (0.32, 10.8)		4.33 (0.13, 9.61)
Mean (SD) PSA ng/ml	277 (937)		148 (438)
Median (range) PSA ng/ml	27.8 (1.9, 6206)		15.6 (3, 2829)
Prostate cancer stage n (%)			
Localised	24 (29)		32 (33)
Locally advanced	30 (37)		23 (24)
Metastatic	22 (27)		31 (32)
Not classifiable	6 (7)		11 (11)
Gleason score n (%)			
2-6	17 (21)		16 (16)
7	24 (29)		31 (32)
8-10	41 (50)		50 (52)
Mean (SD) IPSS total	14.3 (6.91)		13.4 (7.36)
Mean (SD) IPSS QoL score	2.85 (1.62)		2.73 (1.66)
Total prostate volume (ml)	54.8 (26)		49.9 (15.5)
Mean (SD) days since prostate cancer diagnosis	89 (217)		102 (270)
Trial CS35	**Degarelix (n=565)**		**Goserelin (n=282)**
Mean (SD) age (years)	71.9 (8.32)		71.1 (7.9)
Mean (SD) testosterone ng/ml	4.72 (2.01)		4.92 (1.94)
Baseline PSA, n (%)			
0-10	163 (29)		96
10-20	125 (22)		48
20-50	105 (19)		62
≥50	170 (30)		76
Prostate cancer stage n (%)			
Localised	165 (29)		90 (32)
Locally advanced	152 (27)		74 (26)
Metastatic	172 (30)		71 (25)
Not classifiable	76 (13)		47 (17)
Gleason score n (%)			
2-4	49 (9)	16 (6)	
5-6	187 (33)	89 (32)	
7-10	324 (58)	177 (63)	
Trial CS37	**Degarelix intermittent (n=175)**	**Degarelix continuous (n=50)**	**Leuprorelin (n=178)**
Mean (SD) age (years)	71.9 (8.89)	71.7 (8.14)	71 (8.44)
Prostate cancer stage n (%)			
Localised	65 (37)	17 (34)	60 (34)
Locally advanced	7 (4)	1 (2)	13 (7)
Metastatic	0 (0)	0 (0)	1 (<1)
Not classifiable	103 (59)	32 (64)	104 (58)
Gleason score n (%)			
2-4	4 (2)	1 (2)	3 (2)
5-7	56 (32)	22 (44)	61 (35)
7-10	115 (66)	27 (54)	112 (64)

The number of patients who were screened; enrolled and completed the six included trials of degarelix are reported in Table 9. The table also reports the number of patients included in the

intention to treat (ITT); full analysis set (FAS) and per protocol (PP) analyses and provides the numbers and reasons for drop outs across the trials as reported in pages 58-60 of the MS.

Table 9. Number of patients and attrition reported across the six included RCTS of degarelix

N screened/ randomised	N	Reasons for withdrawals (degarelix)	Reasons for withdrawals (comparator)
CS21			
Screened: 807 Randomised: 620 Degarelix 240/80: n= 210; Degarelix 240/160: n=206; Leuprorelin: n= 204	ITT: 610 FAS: NR PP: 584	Withdrawn before any treatment: n=7 (240/80: n=3) Major protocol violations: n=20 (240/80: n=7) AEs: n=34 (240/80: n=15) Lack of PSA suppression: n=2 (240/80: n=1) Lost to follow-up: n=5 (240/80: n=4) Other reasons: n=44 (240/80: n=22)	Withdrawn before any treatment: n=3 Major protocol violations: n=6 Aes: n=12 Lost to follow-up: n=1 Other reasons: n=19
CS28			
Screened: 62 Randomised: 42 Degarelix n=29; Goserelin n=13	ITT: 42 FAS: 40 PP: 37	Did not meet selection criteria: n=2 Protocol violation: n=1	Fatal AE: n=1
CS30			
Screened: 305 Randomised: 246 Degarelix n=181; Goserelin: n=65	ITT: 246 FAS: 244 PP: 221	Major protocol violations: n=16 Withdrawals: AEs: n=2 Other: n=2	Major protocol violations: n=8 Withdrawals: Protocol violations: n=2 Withdrawal of consent: n=1
CS31			
Screened: 201 Randomised: 182 Degarelix n=84 Goserelin n=98	ITT: 182 FAS: 179 PP: 173	Protocol deviations: n=1 Moved abroad: n=1	Protocol deviations: n=3 AEs: n=1 Death: n=1
CS35			
Screened: 1008 Randomised: 859 Degarelix n=527; Goserelin n=287	ITT: 859 FAS: 847 PP: 831	Self-withdrawal: n=29 Lost to follow-up: n=3 Physician decision: n=5 AEs: n=42 Protocol violation: n=17 Other: n=22	Self-withdrawal: n=16 Lost to follow-up: n=2 Physician decision: n=2 Aes: n=14 Protocol violation: n=8 Other: n=5
CS37			
Screened: 480 Randomised: 409 Degarelix intermittent n=177; Degarelix continuous n=50; Leuprorelin: n=182	ITT: 409 FAS: 403 PP: Phase A: 393; PP Phase B: 323	AEs: n=19 (intermittent: n=14) Protocol violation: n=5 (intermittent: n=5) PSA failure >2 at visit 8: n=14 (intermittent: n=10) PSA failure >2 at other visit: n=3 (intermittent: n=2) Discontinued by PI: n=2 (intermittent: n=2) Lost to follow-up: n=1 (intermittent: n=1) Withdrawn consent: n=8 (intermittent: n=5) Other: n=6 (intermittent: n=5)	AEs: n=18 Protocol violation: n=8 PSA failure >2 at visit 8: n=7 PSA failure >2 at other visit: n=1 Discontinued by PI: n=3 Lost to follow-up: n=3 Withdrawn consent: n=2 Other: n=2

Key: AEs= adverse events; ITT= intention to treat; FAS= full analysis set; PI= principal investigator; PP= per protocol.

The numbers of drop outs were relatively low and equal between groups across the trials. Clinical advice to the ERG stated that these drop-outs rates are reasonable and in line with what may be expected in clinical practice.

4.2.2 The manufacturer's approach to validity assessment for each relevant trial.

All six included trials measured testosterone suppression, using a cut-off target of ≤0.5ng/ml to reflect the testosterone levels achieved through surgical castration. This outcome was the primary endpoint in trials CS21 and CS35. Clinical advisors to the ERG stated that testosterone suppression is a relevant endpoint in hormone-therapy for prostate cancer, and that serum testosterone ≤0.5 ng/ml is an appropriate cut-off point to determine efficacy in hormone therapy. Such biological criteria for measuring response to cancer treatment can be regarded as surrogate outcomes for arguably more patient-relevant clinical endpoints, such as survival.

PSA response was also measured in all trials and the ERG clinical advisors agreed that PSA response is an important outcome in clinical practice. For the most part, PSA response was reported as median change (%) from baseline, although CS21 also reported PSA progression (defined as two consecutive PSA increases of ≥50% and of ≥5 ng/ml compared with the nadir), and CS37 examined the proportion of patients with PSA levels ≤4.0 ng/ml at month 14. Survival (overall and progression-free) were also said to be important outcomes by the clinical advisors to the ERG. However, whilst all studies reported overall survival rates, none of the trials were designed to detect differences in this outcome, and the time horizon of the studies was too short to explore this meaningfully.

The dosages of degarelix were in line with the licensed doses for use in the UK (240mg initiation dose, and 80mg monthly maintenance dose). Clinical advice received by the ERG indicates that the dosages of comparator drugs were broadly acceptable. However, the 3-arm CS21 trial also included one arm in which patients received 160 mg per month, The LHRH agonists were also appropriate: CS28, CS30, and CS31 used goserelin 3.6mg monthly, and CS35 used goserelin 10.8 mg three-monthly. Neither of the leuprorelin trials used UK doses: CS21 used a 7.5 mg per month dose, and CS37 used 22.5mg per three-months. These are considerably higher than the doses one would expect in UK practice, in which monthly regimens are typically 3.75 mg, or 11.25mg per three-months. The leuprorelin doses are more likely to reflect US practice. However, clinical input suggested these higher doses would be unlikely to bias the results in any substantial way.

4.2.3 Describe and critique the statistical approach used within each relevant trial.

The pivotal trial CS21 was powered to show non-inferiority for the primary endpoint of reduction of testosterone to castrate level in those with all stages of prostate cancer requiring ADT. The trial was not powered to make substantive conclusions about the target population as the population included patients with localised and not classifiable prostate cancer. The number of patients in trial CS21 who were reported to have locally advanced or metastatic disease and would be considered relevant to the decision problem was 303 out of 607 which represent 49% of the trial population. Subgroup analyses are used in the economic section of the MS for patients with PSA >20ng/ml which represents 48% of the full trial population. The manufacturer states that these patients are a higher-risk subgroup of the ITT population and are more reflective of the population treated with hormonal therapy in the UK (MS page 7). However, the baseline characteristics and results of the PSA >20ng/ml subgroup are not presented in Section 6 of the MS for evidence of clinical efficacy.

The MS acknowledges the limitation of the inclusion of patients with different stages of prostate cancer in the 6 RCTs (MS page 102). They state *"however, tests for an interaction between the disease state and treatment effect showed that treatment effect is not dependent on the stage of disease."*

[redacted]

[redacted]

These statements contradict the assertion in the MS that treatment effect is not dependent on the stage of disease. Therefore the limitation remains that the inclusion of all stages of prostate cancer in the full trial population potentially restricts the generalizability of the results to the target population in the decision problem and the assertion that treatment effect is not dependent on stage of disease is not substantiated by the evidence presented.

The statistical hypotheses tested are described on page 55 of the MS. For the two trials that used testosterone levels as the primary outcome (CS21 and CS35) the following criterion were used:

- FDA criterion – degarelix response rate estimation: this non-comparative primary objective was met if the lower limit of the obtained 95% two-sided confidence interval (CI) was >90%; that is, if the one-year suppression rate was of statistical significance greater than 90%.

- EMA criterion – non-inferiority assessment: in CS21, the non-inferiority limit was –10 percentage points for the difference between degarelix and leuprorelin in the cumulative probability of testosterone ≤0.5 ng/ml from Day 28 to Day 364. In CS35, the pooled standard error (SE) was used to construct the 95% two-sided CI of the difference between degarelix and goserelin in cumulative probability of testosterone ≤0.5 ng/ml from Day 3 to Day 364, and non-inferiority was to be claimed if the lower limit of this CI was >–Δ (change), where Δ=5% was the non-inferiority margin. Full descriptions of the statistical analyses in the randomised controlled trials can be found in Appendix B (Table B6) of the MS.

The main objectives from the included trials are summarised in Table 10.

Table 10. Summary table of main objectives of each of the 6 RCTs, modified from Table 36 (Appendix B of the MS).

Trial no	Hypothesis objective
CS21[9]	• Lower limit of 95% CI for cumulative probability of testosterone being ≤0.5 ng/ml from Day 28 to Day 364 for degarelix was ≥90% • Degarelix was not inferior to leuprorelin for cumulative probability of testosterone levels being ≥0.5 ng/ml from Day 28 to Day 364 days • Non-inferiority margin for difference between treatments was –10%
CS28[11]	• To demonstrate relief of LUTS with degarelix is non-inferior to that with goserelin + bicalutamide, based on reduction in IPSS at 12 weeks compared with baseline • Trial was positive if treatment contrast of degarelix vs goserelin + bicalutamide in mean change from baseline in total IPSS (adjusted for baseline total IPSS, age and country) was statistically significantly smaller (two-sided at α=0.05 level) than Δ=3

Trial no	Hypothesis objective
	points in both FAS and PP analysis set
CS30[13]	• To demonstrate that mean percentage reduction in prostate volume with degarelix is non-inferior to that achieved with goserelin + bicalutamide, based on TRUS at 12 weeks compared with baseline • Non-inferiority was to be established if treatment difference in mean percentage reduction in prostate volume (adjusted for baseline volume and baseline total IPSS) was significantly greater (two-sided at α=0.05 level) than Δ=–10 points (non-inferiority margin) in both FAS and PP analysis set
CS31[15]	• Treatment with degarelix in terms of mean percentage reduction in prostate volume measured with TRUS is non-inferior to treatment with goserelin + bicalutamide at 12 weeks compared with baseline • Non-inferiority was to be established if treatment difference in mean percentage reduction in TPV (adjusted for baseline volume and baseline total IPSS) was significantly greater (two-sided at α=0.05 level) than Δ=–10 points (non-inferiority margin) in both FAS and PP analysis set
CS35[17]	• To demonstrate that degarelix is effective with respect to achieving and maintaining testosterone suppression to castrate levels, evaluated as proportion of patients with testosterone suppression ≤0.5 ng/ml from Day 28 to Day 364 • 95% two-sided CI of difference between degarelix and goserelin in cumulative suppression rate probabilities from Day 3 to Day 364 was constructed using pooled SEs • Non-inferiority was to be claimed if lower limit of CI was >–Δ, where Δ=5% was non-inferiority margin
CS37[18]	• Primary efficacy analysis was examination of non-inferiority of intermittent treatment compared to continuous treatment

It was not clear how pooling of data from different trials was conducted in each of the pooled analyses in the MS (including PSA response, page 70; s-ALP, page 72; testosterone ≤.5ng/ml, page 74). The manufacturer refers to a "number of *post hoc* exploratory analyses of individual patient-level data from the pooled results" (MS page 11) but the raw data were not provided in the MS to demonstrate how the data were combined. The ERG considers that the simple pooling of data may yield counterintuitive or spurious results due to a phenomenon known as Simpson's paradox,[21] a more valid approach would have been to undertake a meta-analysis of the included data. Simple pooling ignores the characteristics of individual studies and relies on the assumption that there is no difference between individual studies. Furthermore, pooling ignores the validity of comparisons made in the individual studies.[22,23] Meta-analysis maintains the effects of randomisation and ensures that each study acts as its own control, minimising the impact of potential confounding variables.[24] Results obtained from a meta-analysis can show a considerable difference from those obtained by simply pooling the same data.[22,25]. Bravata and Olkin[23] strongly recommended that simple pooling should be avoided where possible. During the clarification process the ERG requested the manufacturer to provide full details of methods, data description and results for pooled analyses including:

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

The manufacturer responded with some details including the trials used for each pooled analysis but without justification why meta-analysis was not performed to combine the results from difference trials.

The MS states that pooled data from CS21 and CS35 indicate that LHRH agonist treatment combined with anti-androgen protection against testosterone flare did not achieve the same level of disease control as degarelix during the first year of therapy, even when the 7.5 mg monthly regimen of leuprorelin (which is higher than the 3.75 mg dose indicated for use in the UK) was evaluated (CS21) (page 102). It should be noted that this evidence is based on the selection of the pooled degarelix population (n= 974) with the pooled LHRH agonist population (n=69) which accounts for 66% and 4.7% respectively of the entire pooled population of 1457 patients. Based on the imbalanced group numbers alone, this *post hoc* comparison is inappropriate. Additionally, trial CS21 used a monthly regimen and CS35 used 3-monthly regimen and therefore the simple pooling approach for two different treatments is biased. In addition to the flawed method of simple pooling, there were significant differences in the baseline characteristics of these two groups. Significantly more patients in the degarelix group had localised disease and more patients in the LHRH agonist plus anti-androgen group

had metastatic disease. There were significant differences in Gleason scores between groups and significantly different PSA scores at baseline. The ERG considers that this analysis is inappropriate and the results should be interpreted with caution.

4.2.4 The manufacturer's approach to outcome selection within each trial

Table 11 documents the outcomes and primary endpoints measured in the six included RCTs for degarelix. The primary outcome in trials CS21 and CS35 is testosterone response which is defined as suppression of serum testosterone levels to ≤0.5 ng/ml (castrate level) between Day 28 and 364.

Table 11. Main outcome measures in included randomised controlled trials replicated from page 52 of the MS

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

The clinical advisors to the ERG suggested that trials of androgen deprivation therapy in this stage of prostate cancer and which take place over a relatively short duration are not adequately designed to capture meaningful differences in survival rates between drugs. It was stated that a trial of survival has yet to be conducted and a long-term trial (at least five years in duration) is necessary to examine this. Therefore whilst the manufacturer draws conclusions about overall survival between degarelix and comparators based on mortality rates observed within the trials in the MS, these conclusions should be interpreted with caution.

Additionally clinical input to the ERG suggested that it is unclear whether delay in PSA progression translates to improved survival. Minimal data exist demonstrating an effect of ADT on prostate cancer survival. Clinical advice to the ERG is that orchidectomy can be regarded as the gold standard in terms of control of symptoms and cost-effectiveness for

patients with impending spinal cord compression for this group. LHRH agonists which are essentially designed to simulate surgical castration have additional problems of testosterone flare and the delayed onset of achieving castrate-levels. Thus while degarelix may offer clinical benefit over LHRH agonists in this setting, the benefit of degarelix or LHRH agonists over orchidectomy is unproven. However it was noted that there is significant resistance to orchidectomy amongst both clinicians and patients.

The data for progression-free survival (PFS) from trial CS21 are presented as Kaplan Meier Figures B1 and B3 in Appendix B without further narrative. The MS refers to the Tombal *et al* (2010)[26] published paper. Disease progression is defined in the MS as PSA progression (recurrence/failure) or death. PSA recurrence was defined as two consecutive PSA increases of 50% or greater vs. nadir and 5ng/ml or greater on two consecutive measurements at least 2 weeks apart with the endpoint recorded on the date of the second measurement in the CS21 trial. The MS describes "disease progression" (defined as PSA progression (recurrence/failure), death from any cause or the introduction of additional therapy related to prostate cancer, whichever occurred first for trials CS35 and CS37) on page 71. The MS also states the PSA PFS from the CS21A extension trial (MS page 90).

Time to PSA progression is listed as a relevant outcome in the NICE scope and is reported in the MS only for those who have progressed in the subgroup PSA >20ng/ml in trial CS21. PSA progression rates are reported at one time point only (the end of the study). Progression/recurrence was defined as *"the number of days from first dosing where an increase in serum PSA of ≥50% from nadir and at least 5 ng/mL measured on two consecutive occasions at least two weeks apart was noted. The second occasion was the timepoint of meeting the criterion"* (from the CSR for CS21).

Clinical advice to the ERG highlighted an increasing focus in this field on the correlative relationship between traditional ADT with LHRH agonists and an increase in CVD mortality/morbidity.[27] It was stated that cardiovascular events have been found to be more common with LHRH agonist treatment than with orchidectomy in observational studies and that a retrospective review of all studies comparing degarelix with LHRH agonists suggested a reduced number of adverse cardiac events in the degarelix group.[13] Approximately a third of men on long-term ADT die of cardiovascular disease and a third of progressive prostate cancer.[14] However, evidence of a causal relationship is yet to be demonstrated. Accordingly the MS presents a *post hoc* subgroup analysis for those assessed to be at higher cardiovascular risk at baseline. Clinical advice to the ERG suggests that prospective long-term trials of degarelix and LHRH agonists are required to examine whether pre-existing cardiovascular co-

morbidity could potentially put men at increased risk with androgen deprivation therapy. Additionally trials conducted in more severe disease including those with spinal cord compression and trials in elderly and frail men are also required to examine the benefits of degarelix versus LHRH agonists in this key population who would be unfit for general anaesthesia or have relative contraindications to peripheral anti-androgens used in conjunction with LHRH agonists to prevent flare.

4.2.5 Results from clinical effectiveness review

As discussed in Section 4.1.2, all 6 RCTS of degarelix included patients with all stages of prostate cancer which is discrepant from the target population of advanced hormone-dependent prostate cancer. However, for the base case analysis, the manufacturer uses patients from trial CS21 with PSA >20 ng/ml as a subgroup to represent the target population.

Testosterone response outcome

Table 12. Testosterone outcomes results reported from individual trials in the MS

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	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.

As documented in Table 13, in CS21 the primary endpoint of cumulative probability testosterone levels (95% CI) ≤0.5 from Day 28 to Day 364 to demonstrate non-inferiority of degarelix to leuprorelin was achieved.

Page 65 of the MS states that a secondary outcome, testosterone response (cumulative probability of testosterone levels ≤0.5 ng/ml from Day 28 to 84) was also measured in three other RCTs that compared a monthly maintenance regimen of degarelix 240/80 mg with LHRH agonist treatment (CS28, CS30 and CS31).

Raw data from four RCTs (CS21, CS28, CS30 and CS31) were combined into a pooled dataset, and the Kaplan Meier method was used to estimate the pooled cumulative probability of testosterone levels ≤0.5 ng/ml from Day 28 to Day 84 or Day 364 (MS page 74). The pooled cumulative probability of testosterone levels ≤0.5 ng/ml from Day 28 to Day 84 was 98.0% (95% CI 96.2% to 98.9%) for degarelix 240/80 mg and 96.2% (95% CI 93.7% to 97.7%) for LHRH agonist treatments. The cumulative probability from Day 28 to Day 364 was 95.7% (95% CI 92.4% to 97.6%) for degarelix 240/80 mg and 94.7% (95% CI 91.4% to 96.7%) for LHRH agonist treatments.

Table 13. Kaplan–Meier estimated cumulative probability of testosterone ≤0.5 ng/ml, combining data from CS21, CS28, CS30 and CS31 replicated from page 74 of the MS

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

Table 14. Kaplan Meier estimated cumulative probability of testosterone ≤0.5 ng/ml replicated from MS page 64

Study	Intervention	Duration	Estimate (95% CI)
Monthly maintenance dosing regimens			
CS21[15]	Degarelix 240/80 mg Leuprorelin 7.5 mg Degarelix 240/160 mg Degarelix 240/80 mg Leuprorelin 7.5 mg	Day 28–84 Day 28–84 Day 28–364 Day 28–364 Day 28–364	99.5% (96.5% to 99.9%) 97.6% (92.7% to 99.2%) 98.3% (94.8% to 99.4%) 97.2% (93.5% to 98.8%) 96.4% (92.5% to 98.2%)
CS28 [16]	Degarelix 240/80 mg Goserelin 3.6 mg + bicalutamide	Day 28–84 Day 28–84	100% 92%
CS30 [17]	Degarelix 240/80 mg Goserelin 3.6 mg + bicalutamide	Day 28–84 Day 28–84	96.0% (91.8% to 98.1%) 92.0% (81.9% to 96.6%)
CS31[18]	Degarelix 240/80 mg Goserelin 3.6 mg + bicalutamide	Day 28–84 Day 28–84	97.6% (90.6% to 99.4%) 95.9% (89.4% to 98.4%)
Three-monthly maintenance dosing regimen			
CS35	Degarelix 240/480 mg Goserelin 3.6/10.8 mg	Day 28–364 Day 28–364	90.0% (87.0% to 92.3%) 96.7% (93.7% to 98.2%)

Key: CI = confidence interval

PSA response outcome

The PSA response was measured in trials CS21; CS28; CS30; CS31 and CS35.

Table 15. 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% (IR –92% to –71%)	–66% (–83 to –49%) for goserelin	p<0.0001)
At day 84 & day 364 in CS35	94% 96%	94% 98%	NR

IR- Interquartile range

Table 16. PSA progression in CS21 (PSA >20.ng/ml subgroup) and in CS35

Outcome reported	Degarelix	Comparator	Statistical difference
Proportion with baseline PSA >20 ng/ml who experienced PSA progression in CS21	16.0% (16/100)	28.0% (26/93)	p=0.04
Cumulative probabilities of no PSA progression (recurrence/failure) from Day 0 to Day 364 in CS35	86.5% (95% CI 83.2% to 89.2%)	86.5% (81.7% to 90.1%)	NR

Table 17 Kaplan Meier analysis for the cumulative probability of completing the study without PSA failure from Day 0 to Day 364: ITT analysis set replicated from page 69 of the MS

	Degarelix 240/160 mg				Degarelix 240/80 mg				Leuprorelin 7.5 mg			
	No. at risk	**PSA failure[a]**	**No of censured observations**	**%**	**No. at risk**	**PSA failure[a]**	**No of censured observations**	**%**	**No. at risk**	**PSA failure[a]**	**No of censured observations**	**%**
ITT analysis set	202				207				201			
Day 0 to 28	193	1	8	99.5	201	0	6	100	194	1	5	99.5
To Day 56	192	1	1	99.5	197	0	4	100	192	1	2	99.5
To Day 84	190	1	2	99.5	193	0	4	100	190	1	2	99.5
To Day 112	190	1	0	99.5	189	1	3	99.5	188	3	0	98.4
To Day 140	187	2	2	99.0	187	2	1	99.0	182	7	2	96.4
To Day 168	179	7	3	96.3	185	4	0	97.9	180	9	0	95.3
To Day 196	173	11	2	94.2	181	4	4	97.9	175	11	3	94.2
To Day 224	168	14	2	92.5	175	7	3	96.3	173	12	1	93.7
To Day 252	165	16	1	91.4	169	9	4	95.2	168	14	3	92.6
To Day 280	157	20	4	89.2	165	11	2	94.0	163	18	1	90.4
To Day 308	153	23	1	87.5	161	12	3	93.5	156	21	4	88.7
To Day 336	149	26	1	85.8	156	15	2	91.7	150	24	3	87.0
To Day 364	0	26	149	85.8	0	16	155	91.1	0	26	148	85.9
95% CI	(79.8 to 90.1%)				(85.9 to 94.5)				(79.9 to 90.2)			

Key: CI: confidence interval; ITT = intention-to-treat; PSA = prostate-specific antigen

NB Within-treatment group 95% CI calculated by log-log transformation of survivor function

[a] PSA failure = two consecutive increases in PSA from nadir ≥50% and >5 ng/ml at least two weeks apart

Table 18. *Post hoc* exploratory subgroup analyses of PSA from trial CS21

Outcome reported	Degarelix	Comparator	Statistical difference
Proportion of patients with baseline PSA >20 ng/ml who experienced PSA progression	16.0% (16/100) 240/80 mg	28.0% (26/93) in the leuprorelin group	p=0.04
Median percentage change in PSA levels from baseline to Day 14	-63.4% (IR –77.1% to –48.4%) 240/80 mg	–17.9% (IR–35.5% to –5.2%) in the leuprorelin group	p<0.0001
Median percentage change in PSA levels at Day 28	–84.9% (interquartile range –91.6% to –73.2%) 240/80 mg	–66.7% (interquartile range –81.3% to –47.7%) in the leuprorelin group	p<0.0001

The MS states on page 63 that flare in those patients that did receive flare protection was lower (72.7%) compared with those who did not use anti-androgen therapy (80.9%).

However the CSR for trial CS21 states that *"in the leuprolide 7.5 mg group, a greater median percentage change in PSA levels from baseline was observed for patients who received anti-androgen therapy compared with those who did not. For patients who started anti-androgen therapy on or before Day 7, median PSA levels were reduced by 61.7% on Day 14 and 89.1% on Day 28. In contrast, median PSA levels were only reduced by 15.3% on Day 14 and 61.7% on Day 28 for patients not on anti-androgens. The median percentage change in PSA levels from baseline for patients in the leuprolide 7.5 mg group who received anti-androgen therapy was similar to that observed for patients treated with degarelix."*(Page 96 of the CSR for CS21). These results are not discussed in the MS.

***Post hoc* PSA subgroup results taking into account anti-androgen flare protection from: Results of the pooled analyses from the trials CS21 and CS35**

The PSA PFS failure rate for degarelix (n=974) versus comparator comparators (n=69) was reported. A hazard ratio of 0.500 was reported to be statistically significant p=0.0073.

It is not clear why data were pooled from trials CS21 and CS35 for this comparison considering that trial CS35 uses an unlicensed, intermittent (240mg/ 3-monthly 480mg) dose and the comparators were different (leuprorelin and goserelin respectively). Page 70 of the MS states *"in patients with metastatic disease, mean percentage PSA reduction was greater in those receiving degarelix than those receiving an LHRH agonist plus anti-androgen during the first seven months."* However, the data for this metastatic subgroup are not provided.

It therefore appears that the inappropriately pooled analysis from trials CS21 and CS35 results in a less favourable portrayal of PSA levels for those who received flare protection in the comparator LHRH-agonist group than the subgroup analysis from trial CS21 for patients who received anti-androgen flare protection reported in the CSR.

International Prostate Symptom Score (IPSS) outcome

Table 19. Mean change in total IPSS

Outcome reported	Degarelix	Comparator	Statistical difference
Full analysis set* at week 12 in CS28	–11.2	–7.69 in the goserelin plus bicalutamide group	p=0.197
Full analysis set** at week 12 in CS30	–1.71	0.11 with goserelin plus bicalutamide	p=0.044
at week 12 in CS31	–4.39	–2.74 in the goserelin plus bicalutamide group	p=0.15
At week 4 in CS35	–1.06 (SE 6.27)	–0.211 (SE 6.22) in the goserelin group	p=0.056

* A statistical difference was found for the per protocol analysis
**No statistical difference was observed for the per protocol analysis

Table 19 show a significant difference was found for the IPSS outcome in trial CS30 using the full analysis set (FAS) in favour of degarelix. This difference as not found in the per protocol (PPP) analysis. Conversely no significant difference was found using the PP analysis. In both significant results the p values are borderline and substantive conclusions cannot be made based on either the full analysis set or per protocol analysis.

Serum alkaline phosphatase (s-ALP) outcome

Results are not presented clearly between groups for this outcome but the narrative presented on page 72 of the MS is copied directly from a published paper.[28]

A difference in s-ALP suppression in patients with metastatic prostate cancer in CS21 for degarelix (96 IU/l) versus leuprorelin (179 IU/l) reports a significant difference (p=0.014). Also the MS states that *"pooled data for 2,328 patients from six RCTs (CS21, CS28, CS30, CS31, CS35 and CS37) found that s-ALP levels in patients with metastatic disease were suppressed to a greater extent throughout one-year treatment by degarelix (p=0.0383). The mean adjusted change from baseline was significantly lower throughout 12 months."* Evidently for this pooled analysis, only the significant finding from a *post hoc* subgroup analysis of patients with metastatic disease was reported. This analysis was not defined *a*

priori; the baseline characteristics for this subgroup are not presented and should be interpreted with caution.

Death outcome

Table 20. Death outcome results from included RCTS modified from page 71 of the MS

Trial	Intervention	Deaths/N (%)	Trial duration
CS21[15]	Degarelix 240/160 mg Degarelix 240/80 mg Leuprorelin 7.5 mg	5/202 (2) 5/207 (2) 9/201 (4)	12 months
CS28[16]	Degarelix 240/80 mg Goserelin 3.6 mg + bicalutamide	0/27 (0) 1/13 (7.7)	3 months
CS30[17]	Degarelix 240/80 mg Goserelin 3.6 mg + bicalutamide	0/181 (0) 0/64 (0)	3 months
CS31[18]	Degarelix 240/80 mg Goserelin 3.6 mg + bicalutamide	0/84 (0) 1/98 (1.0)	3 months
CS35	Degarelix 240/480 mg Goserelin 3.6/10.8 mg	8/565 (1) 8/283 (3)	10 months
CS37	Degarelix intermittent 240/80mg Degarelix continuous 240/80mg Leuprorelin continuous 7.5/22.5 mg	2/175 (1) 0/50 (0) 2/178 (1)	7-14 months

As documented in Table 20 and noted previously, due to the short follow-up in the included trials the numbers of deaths are low and therefore it is difficult to draw substantive comments about mortality from the trials based on these figures.

Quality of life

Table 21. Quality of life measures measured and reported from included RCTs extracted from pages 72/73 of the MS

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.		

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
FACT-P: Functional Assessment of Cancer Therapy-Prostate
SF-12 v2: Short form- 12 item survey version 2
SF-36 v2: Short-form- 36 item survey version 2
VAS: Visual Analogue Scale

Table 21 shows that no significant differences were observed on quality of life outcomes in trials CS21; CS28; CS30; CS31; or CS37 between degarelix and the comparator arms. In trial CS35 the MS reported a significantly greater decrease in the degarelix arm for the VAS however as noted previously, this trial is not deemed as relevant to the decision problem.

4.2.6 Results from meta-analyses carried out by the manufacturer.

The MS lists eight outcomes measured in the 6 RCTs (Table 11, page 52). However, three of these outcomes (PFS; health-related QoL; and adverse events) were missing from the meta-analysis section. The MS states that meta-analyses were completed for the following outcomes: testosterone response; prostate size reduction; IPSS; PSA response; and overall

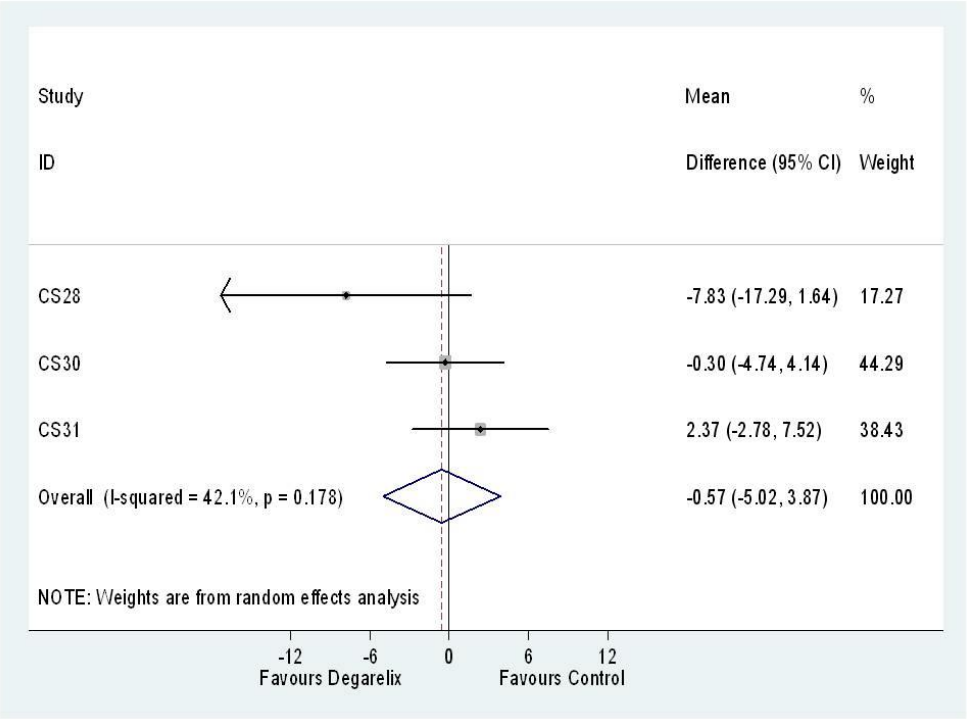
survival (MS page 80). However the analysis for the cumulative probability of testosterone levels ≤ 0.5ng/ml presented in the MS used simple pooling of all the data from different studies. No formal meta-analysis was used for this outcome measure in the MS but a meta-analysis was subsequently provided by the manufacturer in the clarification letter. It is not clear what statistical method and software were used for all meta-analyses in the MS. Meta-analyses are presented in the MS for:

i. prostate size reduction;
ii. IPSS;
iii. PSA response;
iv. overall survival.

Reduction in prostate size

The percentage change in prostate volume from baseline to Day 84 (Week 12) was evaluated in the three RCTs of a 3-month duration (CS28, CS30 and CS31; MS page 75). The differences between degarelix and control treatment in percentage change in prostate volume recorded in the three 3-month RCTs were combined in a meta-analysis (see Figure 3), using the reported adjusted differences and 95% CIs from the clinical study reports. No statistically significant heterogeneity was observed across the three studies, although the I-squared statistic is moderately high (I2=42%; p=0.178).

Figure 3. Difference between degarelix and control treatment in percentage change of prostate volume from baseline to Day 84 (Week 12) replicated from page 75 of the MS



The conclusion for the meta-analysis of reduction in prostate size in the MS was *"The pooled mean difference between degarelix and LHRH agonists was -0.57 (95% CI –5.02 to 3.87), indicating that degarelix is non-inferior to leuprorelin or goserelin plus bicalutamide."*
However, the included studies only compared degarelix against goserelin and therefore the result stated by the manufacturer about degarelix versus LHRH agonists is too broad.

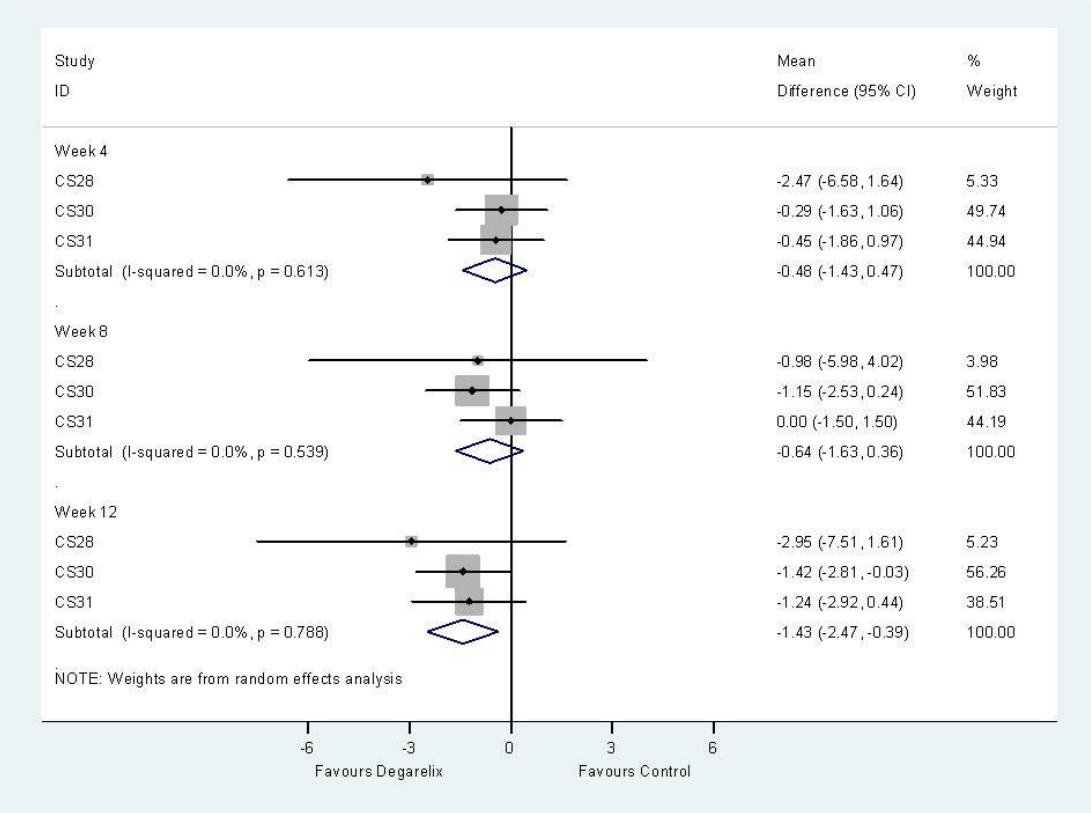
IPSS

A meta-analysis is presented on page 75 of the MS. The MS states that the IPSS is used to assess the severity of lower urinary tract symptoms (LUTS) and to monitor the progress of the disease process once treatment has been initiated. A higher overall score indicates increased severity of LUTS, so a reduction in IPSS indicates improvement in LUTS.

Three RCTs (CS28, CS30 and CS31) measured change in IPSS from baseline. The meta-analysis was conducted, using the reported mean estimates of change and 95% CIs at weeks 4, 8 and 12 (see Figure 11). No significant heterogeneity was observed across studies (I^2=0.0%; p=0.613, p=0.539 and p=0.788 at Weeks 4, 8 and 12, respectively). The pooled difference in change from baseline in IPSS was –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 difference between degarelix and LHRH agonist control, thus, tended to increase over time and was statistically significant at Week 12. As with the reduction in prostate size outcome the included studies only compared degarelix against goserelin and therefore the conclusion stated by the manufacturer about degarelix versus LHRH agonists is too broad.

Figure 4. Difference between degarelix and control treatment in change from baseline in international prostate symptom score (IPSS) replicated from page 76 of the MS

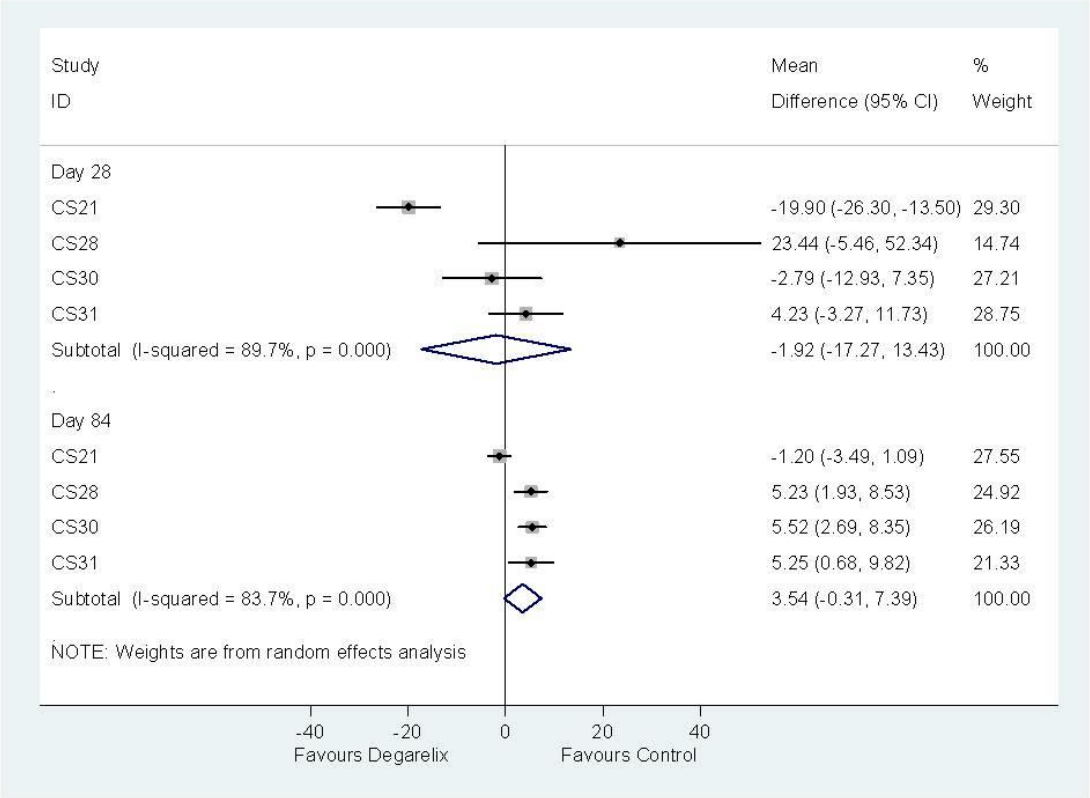


PSA response meta-analysis

The manufacturer presents a meta-analysis (MS page 76/77) using data from the RCTs that compared a monthly maintenance regimen (240/80 mg) of degarelix with monthly maintenance LHRH agonist therapy (CS21, CS28, CS30 and CS31). The manufacturer describes:

"For percentage change in PSA levels, the pooled mean difference between degarelix and LHRH agonists was –1.92 (95% CI –17.27 to 13.43; p=0.806) at Day 28 and 3.54 (–0.31 to 7.39; p=0.072) at Day 84. However, statistically significant heterogeneity between the individual RCTs was detected (I^2=89.7% at Day 28 and I2=83.7% at Day 84; p<0.001)."

Figure 5. Meta-analysis of percentage change in PSA from baseline replicated from page 77 of the MS



However, as highlighted by the manufacturer, the results of this meta-analysis for the percentage change in PSA levels should be interpreted with caution for a number of reasons. First, significant heterogeneity is suggested by the manufacturer to arise as a consequence of the differences in the baseline PSA level due to different eligibility criteria in the four studies. Trial CS28 included patients with much higher baseline PSA levels (median PSA levels: 41–55 ng/ml) than the other three RCTs (median PSA levels: 17–20 ng/ml in CS21; 10 ng/ml in CS30; and 16–28 ng/ml in CS31). This example further highlights how the use of simple pooling in other analyses would ignore this heterogeneity.

The MS also states that "*in addition, clinical expert opinion indicates that PSA progression, rather than absolute PSA percentage change from baseline, is routinely used in clinical practice as a prognostic indicator for treatment response because it is a more appropriate outcome to measure disease progression when using PSA as a surrogate clinical marker. However, no meta-analyses could be completed for PSA progression, as only one trial that evaluated monthly dosing regimens (CS21) assessed PSA progression (see Section 6.5.3).*"(MS page 76/77). Although it is correct that PSA progression is an important biomarker with which response is evaluated in clinical practice, clinical advice to the ERG stated that PSA progression-free survival has been shown to correlate poorly with overall

survival in men with castrate-resistant metastatic disease.[29] A recent review of prostate cancer biomarkers does not recommend the use of PSA progression as a surrogate endpoint.[29] For PSA progression to be appropriate as a surrogate, its association with survival time should be examined using a statistical measure that allows for censoring in both time to death and biomarker progression, such as the Kendall rank correlation coefficient.[29,30] If a strong association is found, it is recommended that this should be tested in clinical trials.

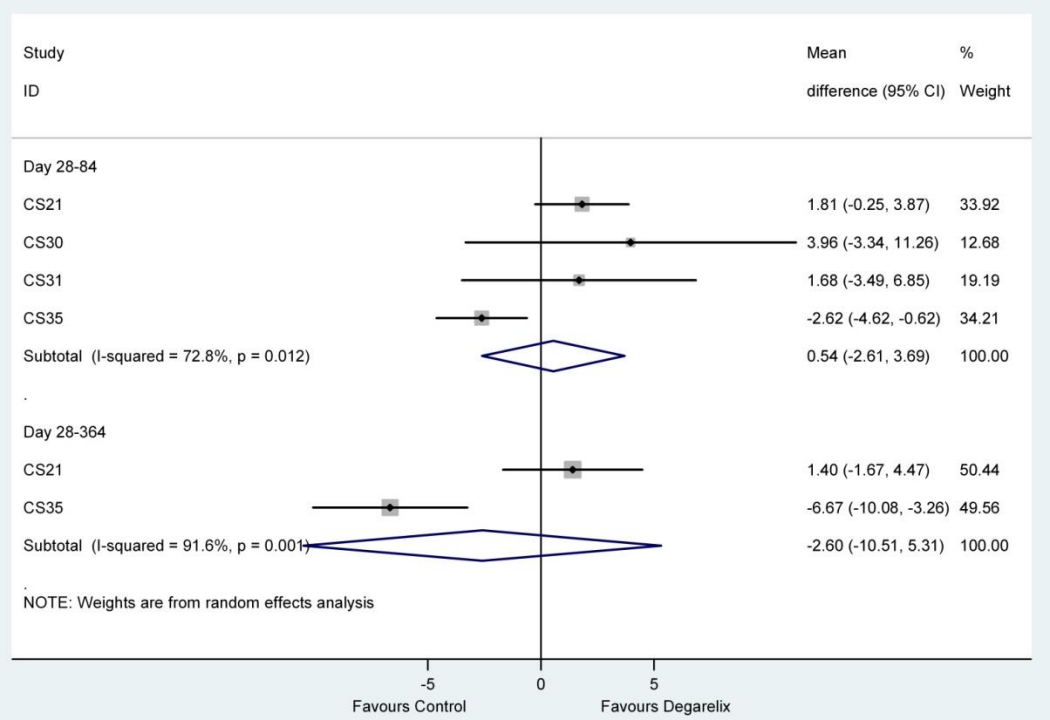
In the meta-analysis of PSA response, no justification has been given for assuming leuprorelin and goserelin have equivalent efficacy. Statistically significant heterogeneity has been reported for this analysis and the baseline PSA level was suggested by the manufacturer to cause this significant heterogeneity. However, no formal meta-regression was performed to justify this.

Additionally the manufacturer reports the mean differences between the treatment groups have been used for this meta-analysis rather than the median values "*as the differences between degarelix and the LHRH agonists were symmetrically distributed*" (MS page 76) but the median PSA values were used when reporting the baseline characteristics and analyses for PSA response in the individual trials (MS pages 69/70). The ERG considers that if the data were symmetrically distributed then the median values from the data reported in section 6.5.3 should be similar to the mean values used for the meta-analysis. However, it is not clear that the mean percentage change values are consistently reflective of the median percentage change. For example, the median percentage difference in trials CS30 at day 28 is -0.6 (MS page 69) and the mean percentage difference change used in the meta-analysis at day 28 is -2.79 (MS page 77). These values are not similar and call into question the manufacturer's interchangeable use of median and mean values in the MS.

Testosterone response

The ERG requested clarification on the selective exclusion of trial CS35 from certain analyses in the MS. The manufacturer responded that "*Data on the cumulative probability of T≤0.5 ng/mL between degarelix and LHRH agonists from Day 28 to 364 were also available from trial CS21 and CS35. The results from the two trials were statistically significantly heterogeneous (I2=92%, P=0.001).*" A forest plot from a meta-analysis that was not presented in the MS was included in the clarification letter and is presented in Figure 6 below.

Figure 6. Meta analyses: difference (%) in cumulative probability of T≤0.5 ng/mL between degarelix and LHRH agonists from Day 28 to 84 submitted by the manufacturer in the clarification letter



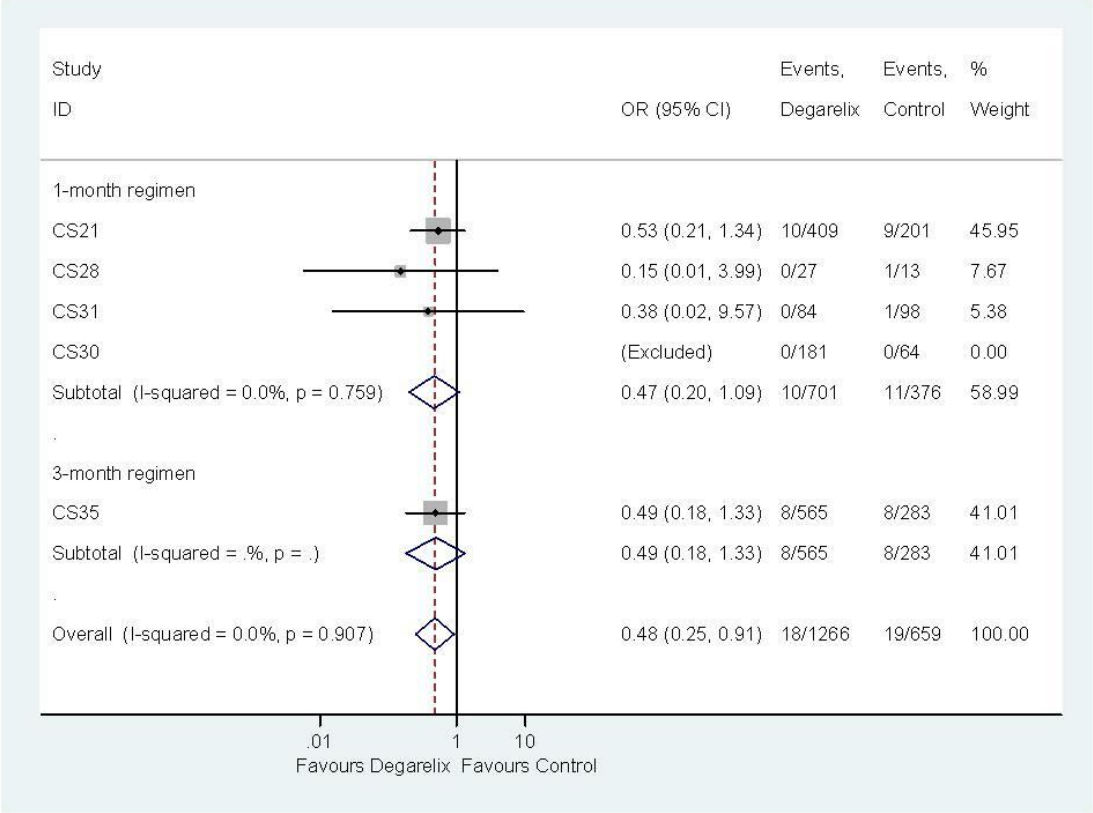
The manufacturer submitted the meta-analysis for testosterone response in response to the ERG's clarification request for the inclusion of trial CS35. The ERG did not recommend the inclusion of trial CS35 but asked for justification of its inclusion. The meta-analysis submitted by the manufacturer unwittingly demonstrates why trial CS35 should not have been included in pooled analyses. The ERG considers that the trial CS35 should have been excluded in these analyses and arguably from the decision problem. The significant heterogeneity observed for this analysis further highlights that pooling data from different trials, particularly when the dosing regimens are discrepant, should be avoided. It additionally highlights that simple pooling would not detect or account for the between-trial heterogeneity demonstrated here. This large heterogeneity could indicate that the two different comparators (leuprorelin and goserelin) are quite different. Therefore when including different treatments, pairwise meta-analysis should also be avoided unless there is evidence showing that these different treatments give identical treatment effects.

Overall survival

In the meta-analysis of overall survival (MS pages 78/79) the manufacturer states that *"Data from CS37 were not used in this meta-analysis, because the degarelix monthly maintenance dose may not be comparable with the leuprorelin three-month regimen."* However, another three-month regimen study CS35 was included in the analysis without any explanation.

Furthermore, the use of odds ratio for this analysis has not been sufficiently justified. Using odds ratios does not take into account the different trial durations: 3 months for CS28; CS30; CS31 and 12 months for CS21.

Figure 7. Meta-analysis of overall survival across trials replicated from page 79 of the MS



The results from all of the meta-analyses need to be interpreted with caution for the following reasons:

- No justification has been given for assuming leuprorelin and goserelin have equivalent efficacy.
- Significant heterogeneity was detected in the meta-analysis of PSA response and formal meta-regression was not performed to justify this.
- Trial CS35 is included in the meta-analysis of overall survival even though it does not use the licensed dose of degarelix (whilst trial CS37 which also used an unlicensed dose of degarelix is excluded).
- The use of odds ratio assumes proportional odds over time across trials of varying duration (between 3 months to 12 months).

- The meta-analysis of overall survival is based on trial data for which the study duration was too short, and not designed to detect differences in survival in this population.

4.2.7 Non-RCT evidence

The manufacturer reported searching for non-RCT evidence in Section 6.8 of the MS (page 89). However, the strategy referred to by the manufacturer (Appendix 10.8.4; MS page 244) was previously described in Section 10.2.4. (MS page 232) where the study design filters were applied to retrieve only RCTs, systematic reviews and meta-analysis studies but not non-RCT trials. Therefore, separate searches for non-RCT evidence were not undertaken by the manufacturer. The manufacturer reported finding non-RCT studies among the collection of records retrieved from the direct and indirect evidence searches. This approach used alone is not considered comprehensive or systematic.

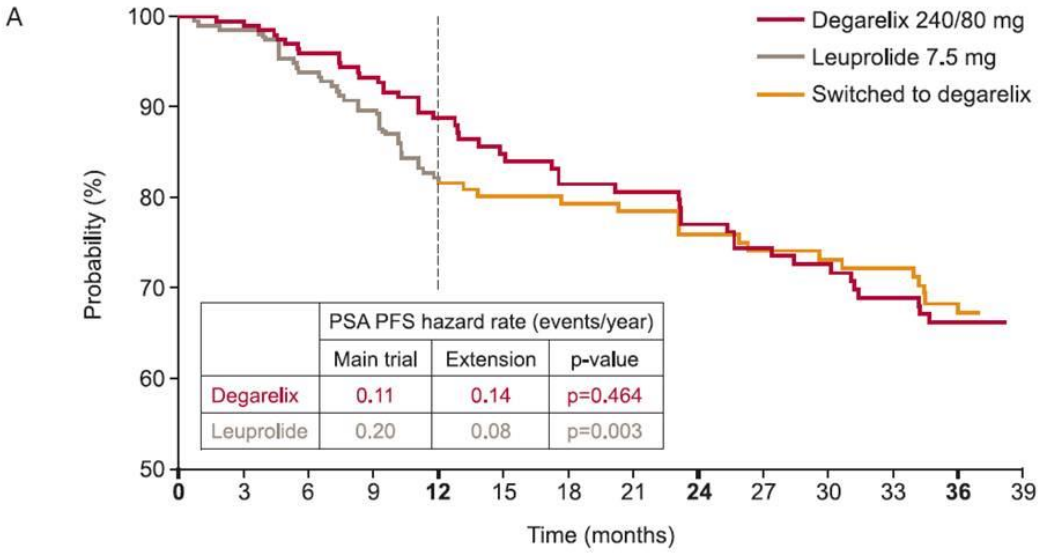
The search strategy for adverse events was integrated in the searches for direct and indirect evidence in Section 10.2.4. Terms for the intervention were combined with known adverse events outcomes and specific adverse effect terms (e.g. adverse effect or side effect). The MS search was further restricted by combining the results with an RCT or systematic/meta-analysis filter. The ERG considers that the conceptual grouping of the terms is too restrictive and non-RCT studies reporting adverse events could have been missed using this approach. The ERG recommends that an appropriate adverse events filter should be used such as the BMJ adverse effects strategy, [31] where the strategy comprises drug terms combined with either the specific adverse events outcomes, adverse events terms (safe or safety or side-effect of undesirable effect of treatment emergent or tolerability or toxicity or ADRs) and drug-related subheadings (e.g. degarelix/ae, to). The ERG carried out separate searches for adverse events (see Appendix 4). Given the large number of records retrieved, it was not possible for the ERG to review during the STA process.

The MS describes that six dose-findings studies were identified (CS02; CS12; CS14; CS15; CS18 and Ozono et al 2012[32]. However as stated in Section 4.1.5 of this report, 12 trials were identified by the ERG which should have been included in this review for non-RCT evidence. Six extension studies are also reported to be included for the non-RCT evidence (CS12A; CS15A; CS21A; CS34; CS35A and CS42A). Three of these are extension trials to the 6 included RCTs (CS21A; CS34 and CS35A). CS21 included a five-year extension phase (CS21A), in which all patients previously treated with leuprorelin were randomised to one of the two degarelix groups. CS34 extended the three-month trials of degarelix (CS28, CS30,

CS31) by up to 22.5 months (mean: 11.7 months), although only 77 patients from the previous trials enrolled. CS35A was an extension of the CS35 trial which was planned to run for up to 40 months (including 13 months' treatment in CS35); however, the extension was terminated early due to insufficient trial enrolment.

The manufacturer presents a narrative of the extension trials including a description of the CS21A extension trial which included 385 patients. This trial was designed to provide evidence for the safety and long-term tolerability of degarelix as it is a single arm trial and all patients switched from leuprorelin to degarelix. Patients in CS21A were followed up for five years, and outcomes were compared between patients who continued degarelix treatment and those who switched from leuprorelin to degarelix. The manufacturer states that *"sustained suppression of both testosterone and PSA levels was observed with degarelix treatment during CS21A, irrespective of whether patients received degarelix or leuprorelin during the main CS21 trial. No statistically significant differences in the number of patients with PSA progression or who escaped testosterone suppression were observed between the treatment groups after switching from leuprorelin to degarelix in CS21A. For patients switched from leuprorelin, degarelix provided more effective suppression of FSH. The PSA PFS hazard rate decreased significantly after the switch in the leuprorelin/degarelix group, while the rate in those who continued on degarelix was consistent with the rate in Year 1"*[33] (MS page 90). The ERG have reviewed the reference provided for this data and considers that the hazard rate is not entirely consistent, with those in the group who switched from leuprorelin to degarelix reaching a slightly lower PSA PFS hazard rate than those who had been receiving degarelix since the beginning of trial CS21.

Figure 8. PSA PFS probability in all patients in extension trial using original CS21 criteria for PSA progression replicated from Crawford *et al*., (2011)[33]



Time (days)	*0*	*84*	*168*	*252*	*336*	*420*	*504*	*588*	*672*	*756*	*840*	*924*	*1008*	*1092*	*1176*
Number of patients at risk															
Degarelix	207	200	187	176	162	109	101	93	91	87	83	79	75	71	67
Leuprolide	201	193	182	174	157	110	102	98	93	85	81	78	74	68	66

As can be seen from Figure 8. the hazard rate for patients who had received leuprorelin in trial CS21 and subsequently switched to degarelix in the extension study had a hazard rate of 0.08 which is also lower than patients who had received degarelix from the beginning to the end of trial CS21 (0.11) and those who continued in the extension trial (0.14). Additionally the Kaplan Meier curves for PSA PFS cross, also possibly indicating that: those who received degarelix later in the treatment sequence did better than those who had initiated treatment with degarelix earlier in the sequence. As patients were not randomly allocated to the two arms there is no guarantee that patients in the degarelix arms who entered the extension study were similar to the patients in the leuprorelin arm who entered the extension study. Whilst the differences in hazard rates are not statistically different these analyses highlight that evidence on the potential benefits of earlier versus later treatment with the intervention is lacking and not explored in the MS.

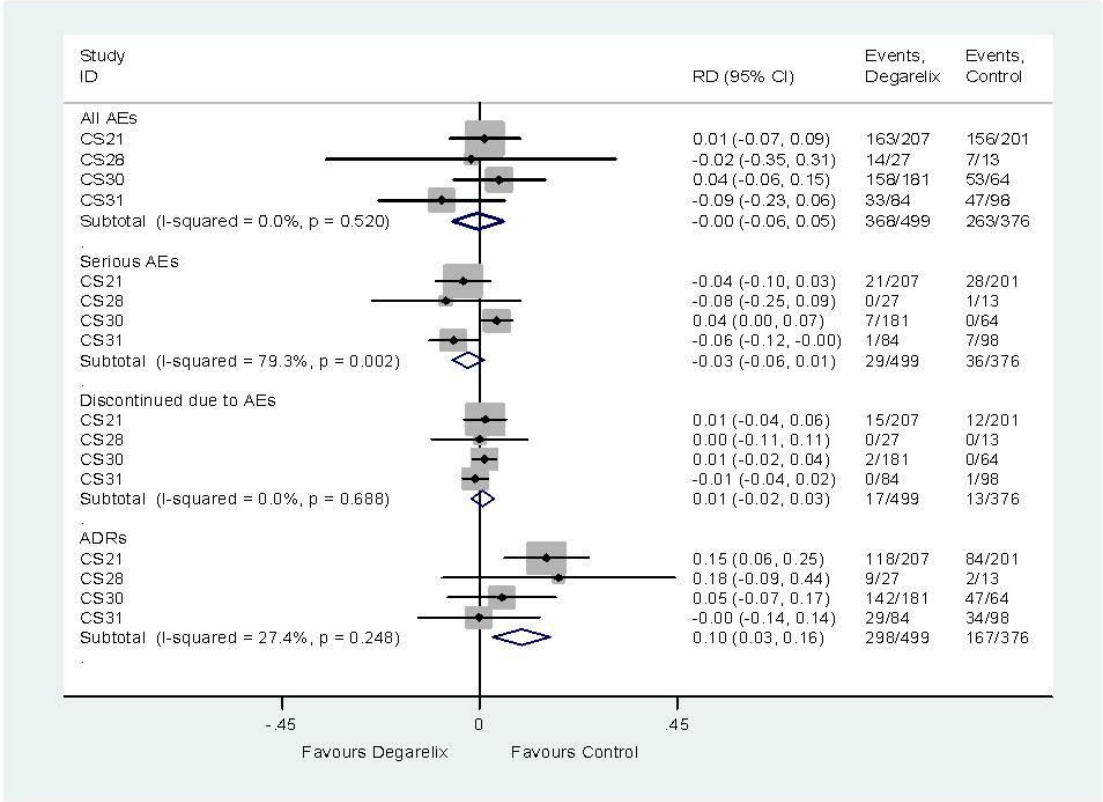
The manufacturer also describes an observational study by Geiges et al (2012)[34] which concludes that *"efficacy and safety of treatment with degarelix was confirmed in routine daily practise. The efficacy of degarelix is comparable with other androgen-deprivation-therapies."* The narrative of the six dose-finding trials and the five other extension trials

provide a brief summary and conclude that degarelix was well tolerated and effective in attaining and sustaining suppression of PSA and testosterone levels.

4.2.8 Adverse Events

The MS presents a meta-analysis of adverse events from the four RCTs (CS21; CS28; CS30; CS31) on pages 93/94 in which degarelix 240/80 mg was compared with leuprorelin or goserelin plus bicalutamide and conclude that overall, no statistically significant difference in the proportion of patients experiencing any AEs, death or serious AEs (SAEs) was observed between the degarelix 240/80 mg group and the LHRH agonist group. The MS further notes however that the "*proportion of patients with ADRs (AEs evaluated by the investigator as possibly or probably related to the IMP) was higher in the degarelix group (rate difference 9.5% [95% CI 3.0% to 16.0%]; p=0.004). The higher rate of ADRs in the degarelix group was caused by injection site-related AEs (such as injection site pain, erythema and swelling). Notably, most of the injection-site reactions with degarelix (240/80mg) in CS21 occurred with the initiation dose and decreased over time (32% of injections were associated with an injection site reaction with the initiation dose, compared with only 3% of injections with the first maintenance dose and 2–5% with subsequent maintenance doses). This is likely to be related to the subcutaneous route of administration and the larger volume administered as the initiation dose versus the maintenance dose. In CS21, the percentage of ADRs remaining after exclusion of injection site-related AEs was evaluated and was found to be similar in the three treatment groups: 44% (88/202) for degarelix 240/160, 43% (90/207) for degarelix 240/80 mg and 42% (84/201) for leuprorelin.*"

Figure 9. Summary adverse events from relevant RCTs (difference in risk [RD] between degarelix and control) replicated from page 94 of the MS



The manufacturer again incorrectly assumes leuprorelin and goserelin are identical in conducting a pair wise meta-analysis. Large heterogeneity was observed in serious adverse events and moderate heterogeneity was found for adverse drug reactions but no explanations have been given.

The MS states that as a consequence of testosterone suppression, hot flushes were the most commonly reported AE in both the degarelix and the LHRH control group. Although the rate of patients with hot flushes varied considerably across trials, the difference in the percentage of patients with hot flushes between groups within each trial was similar. Clinical advice to the ERG was that in ADT serious adverse events are rare. Whilst most adverse events are transient and linked to initiation of ADT, common long-term side effects include: impact on bone health; lower metabolism; cardiovascular risk; sexual dysfunction; gynecomastia; reduction in penile and testicular size; fatigue; hot flashes; anaemia and potential cognitive decline. It may be important to consider that the adverse event profile for the comparators may have been more favourable had anti-androgen flare protection been used consistently in the included trials.

CVD AE subgroup analysis

The manufacturer conducted a *post hoc* pooled analysis of data from 2,328 patients from all six RCTs to compare the risk of cardiovascular events in patients treated with degarelix with those receiving LHRH agonists. Cardiovascular events included were arterial embolic and thrombotic events, haemorrhagic and ischaemic cerebrovascular conditions, myocardial infarction and ischaemic heart disease. An independent academic group is reported to have used Kaplan Meier curves and performed Cox regression model analysis of the pooled data to establish the risk of CVD AEs in the total RCT patient population and in those with a pre-existing CVD at baseline. Pre-existing risk was assessed using the following Standardised MedDRA Queries (SMQs) applied to individual patient medical records: Myocardial infarction (SMQ); Ischaemic cerebrovascular conditions (SMQ) Haemorrhagic cerebrovascular conditions (SMQ); Embolic and thrombotic events, arterial (SMQ); Other ischaemic heart disease (SMQ). The MS states that in total, data from 2,328 patients were analysed; 1,491 received degarelix and 837 received an LHRH agonist (goserelin: n=458; leuprorelin: n=379) (page 97). The treatment groups were balanced for common baseline characteristics and CVD-related characteristics. The following conclusions are drawn:

- Among men with pre-existing CVD, the risk of cardiac events within one year of initiating therapy was significantly lower for those treated with degarelix than for those treated with LHRH agonists (HR 0.44; 95% CI 0.26 to 0.75; p=0.0023).
- Among men with no history of CVD, the incidence of cardiac events within one year was comparable between the two treatment groups.

This pooled analysis indicates that men with a history of CVD, who are in need of androgen deprivation therapy, experience a significantly lower risk of CVD AEs if treated with degarelix compared with an LHRH agonist. The ERG considers that meta-analysis, not simple pooling, should have been conducted for the reasons stated previously in this report. Results from simple pooled analyses should be treated with caution. Clinical advice to the ERG stated that currently the evidence for a link between LHRH agonists and CVD are correlative and there is a lack of prospective level 1 evidence to base conclusions about the potential relationship between these treatments and the cardiovascular risk.

Disease-related adverse events

The same pooled population from the 6 RCTs for the assessment of CVD risk was used to explore disease-related risks including the risk of fractures, joint-related signs and symptoms and urinary tract events (MS page 96). The MS concludes:

- The overall probability of joint-related signs and symptoms was significantly reduced in the degarelix group compared with the LHRH group (5.3% versus 8.1%, respectively; p=0.0116, log-rank).

- The overall probability of fracture was also significantly reduced in the degarelix group compared with the LHRH group (0.9% versus 2.3%, respectively; p=0.0234, log-rank).

- The overall probability of a urinary tract AE was significantly lower in degarelix- versus LHRH agonist-treated patients (15.0% versus 22.3%; p<0.0001, log-rank).

The ERG recommends that results from all pooled analyses should be interpreted with caution.

4.3 Summary and critique of submitted evidence in the MTC

The manufacturer conducted a mixed treatment comparison (MTC) meta-analysis of degarelix with goserelin; leuprorelin; triptorelin; and bicalutamide. It is important to note that the manufacturer did not use this MTC within their *de novo* economic analysis.

4.3.1 Manufacturer's search strategy for the MTC

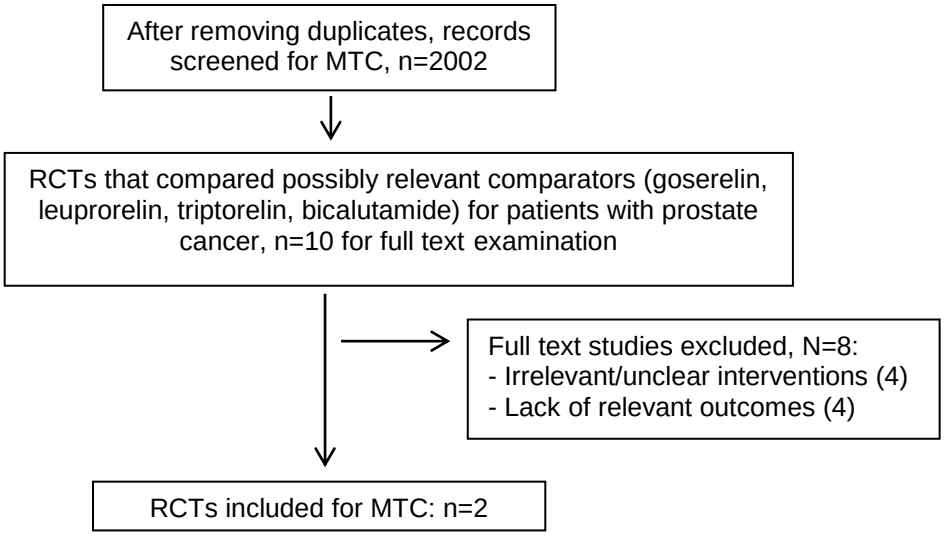
The same searches used to identify evidence for the first systematic review were used to inform the MTC. As mentioned in the search critique of degarelix (MS section 6.1.1.), the manufacturer search strategies only comprises free-text terms without broad and specific subject headings as seen in the cost-effectiveness searches (Section 10.10.4, page 246 of the MS). The broad subject headings include gonadotropin-releasing hormone, hormone antagonists and androgen antagonists whereas, and specific comparator subject headings include: goserelin; leuprolide, triptorelin pamoate and buserelin. The difference in the number of records retrieved in the modified Medline and Embase search strategies were 799 and 654 records, respectively. The ERG did not review the additional records retrieved and therefore were unable to confirm whether studies have been missed.

The terms used in searching the WHO ICTRP database were not given. The ERG additionally searched the ClinicalTrials.gov register for the 44 individual terms for both intervention and comparators. Only 26 unique records were retrieved and reviewed. The ERG did not find any relevant studies that had been missed from the MTC in these unique records.

4.3.2 *Study selection for the MTC and assessment*

The ERG applied the checklist from the NICE Decision Support Unit; Technical Support Document 7[35] to assess the evidence synthesis in the manufacturer's MTC. It was unclear from the MS how the 10 papers that were assessed for inclusion into the MTC (MS pages 82-84) were selected from the 2002 search records from the initial search. The ERG requested clarification from the manufacturer on the inclusion/exclusion criteria for the identification of the studies for the mixed treatment comparison and for the resulting flow diagram depicting the assessment of studies for the MTC. The manufacturer repeated the inclusion criteria for the first systematic review with "intervention" and "comparator" boxes merged. The manufacturer also provided a flow diagram (Figure 10) in their clarification response which did not elucidate the process of how the 2002 studies were assessed for eligibility into the MTC and how the 10 studies were retrieved.

Figure 10. MTC study selection flow diagram provided by the manufacturer in the clarification letter in response to ERG request.



It is not clear from Figure 10 how references were screened for examination at title or abstract stage and subsequently excluded from the MTC. Only ten papers from a database of 2002 records of the five drugs: degarelix; leuprorelin; triptorelin; goserelin and bicalutamide monotherapy were reported to be assessed at full text. The ERG considers that the process of study selection for the MTC was not transparent and it would therefore not be possible to reproduce the manufacturer's process of sifting the 2002 references to establish whether any other papers were missed for inclusion into the MTC.

4.3.3 Studies were included in the MTC

Ten studies were reviewed as full text papers (pages 82-84 of the MS & Table 22 below) and seemingly were rejected for inclusion into the MTC if:

a) The intervention/comparator dose was not consistent with the indications used in the degarelix trials;
b) No survival or PSA survival/recurrence outcomes were reported;
c) The percentage receiving medical versus surgical castration in the "castration group" was unknown;
d) The study reported that less than 50% of the castration group had medical versus surgical castration.

Therefore not all studies that involved at least two of the treatments in the decision problem have been included in the MTC. Some trials were excluded which could have been included in the MTC and excluded in subsequent sensitivity analyses subject to the reasons above. For example the Chodak (1995) and Kaisery (1995) studies could have been included as they report survival but they were excluded from the due to reasons (c) and (d), respectively, above.

Table 22. Eight studies excluded from the MTC; taken from Table 16 of the MS

Study (n)	Interventions compared	Study participants	Outcomes reported	Main conclusions	Reasons for exclusion from MTC
Chodak *et al* (1995) (n=486)[122]	Bicalutamide 50 mg Castration (surgical or goserelin)	Patients with untreated stage D2 prostate cancer	Time to treatment; failure; Objective disease progression; Survival; QoL	Bicalutamide 50 mg was not as effective as castration, but had favourable QoL outcomes and low incidence of non-hormonal AEs	Exclude (percentage of patients that received goserelin in castration group is unknown)
Dias Silva *et al* (2012) (n=60)[123]	Leuprorelin 3.75 mg Leuprorelin 7.5 mg Goserelin 3.6 mg	Patients with advanced prostate cancer, with indication for hormonal therapy	Serum testosterone	Leuprorelin 7.5 mg showed better results in reaching castration levels than leuprorelin 3.75 mg but the difference was non-significant	Exclude (no overall survival or PSA progression [recurrence/failure] outcomes)
Kaisary *et al* (1995) (n=245)[126]	Bicalutamide 50 mg Castration (surgical or goserelin)	Patients with advanced prostate cancer	Time to treatment failure; Time to objective progression; Survival; QoL Tolerability	Survival similar in the two groups; Bicalutamide 50 mg was associated with a low incidence of diarrhoea and sexual dysfunction	Exclude (<50% in castration group received goserelin)

Study (n)	Interventions compared	Study participants	Outcomes reported	Main conclusions	Reasons for exclusion from MTC
Kuhn *et al* (1997) (n=67)[127]	Triptorelin 3.75 mg Leuprorelin 3.75 mg	Patients with prostate cancer not suitable for surgery	Pain; UTI symptoms; Prostate volume; Mean serum PSA; Testosterone level	Triptorelin induced a greater decrease in testosterone levels than leuprorelin	Exclude (leuprorelin 3.75 mg; no survival or PSA recurrence outcomes)
Sieber *et al* (2004) (n=103)[128]	Bicalutamide 150 mg Medical castration	Patients with localised or locally advanced prostate cancer	Bone mineral density; Fat-free mass; Serum lipids	Bicalutamide 150 mg may offer an important advantage compared with castration in bone loss and body composition	Exclude (LHRH agonists not specified; no survival or PSA progression [recurrence/failure] outcomes)
Smith *et al* (2004) (n=52)[129]	Bicalutamide 150 mg Leuprorelin (three-month regimen 22.5mg)	Patients with prostate cancer and no bone metastases	Bone mineral density; Body composition	Bicalutamide increased bone mineral density, lessened fat accumulation and had fewer bothersome side-effects than Leuprorelin	Exclude (leuprorelin three-month regimen; no overall survival or PSA progression [recurrence/failure] outcomes)
Williams *et al* (2003) (crossover, n=50)[130]	Leuprorelin Goserelin	Patients with advanced prostate cancer	Discomfort score	Patients tolerated leuprorelin better than goserelin ($p<0.01$)	Exclude (no overall survival or PSA progression [recurrence/failure] outcomes)
Tyrrell et al 1998 (n=1,453)[131]	Bicalutamide 100 Bicalutamide 150 mg Castration (surgical or goserelin 3.6 mg)	Patients with metastatic (M1) prostate cancer	Time to death; Objective progression; Treatment failure; QoL; Safety	Bicalutamide 150 mg was less effective than castration for survival outcome, but QoL benefit and subjective response compared with castration.	Exclude (proportion of patients who received goserelin in the castration group is unknown)

Key: AE = adverse event; LH = luteinising hormone; LHRH = luteinising hormone-releasing hormone; MTC = mixed-treatment comparison; PSA = prostate-specific antigen; QoL = quality of life; UTI = urinary tract infection

The manufacturer discusses the two trials included in the MTC on pages 85-87 of the MS. One study (Iversen 1998) compared bicalutamide monotherapy (150 mg) versus castration (medical or surgical) and one study (Heyns 2003) compared triptorelin with leuprorelin. Both studies were included in the MTC along with four of the degarelix trials: CS21; CS28; CS30 and CS31 (see Table 23 and Figure 11).

Table 23. Studies Included in the MTC; adapted from Table 16 of the MS

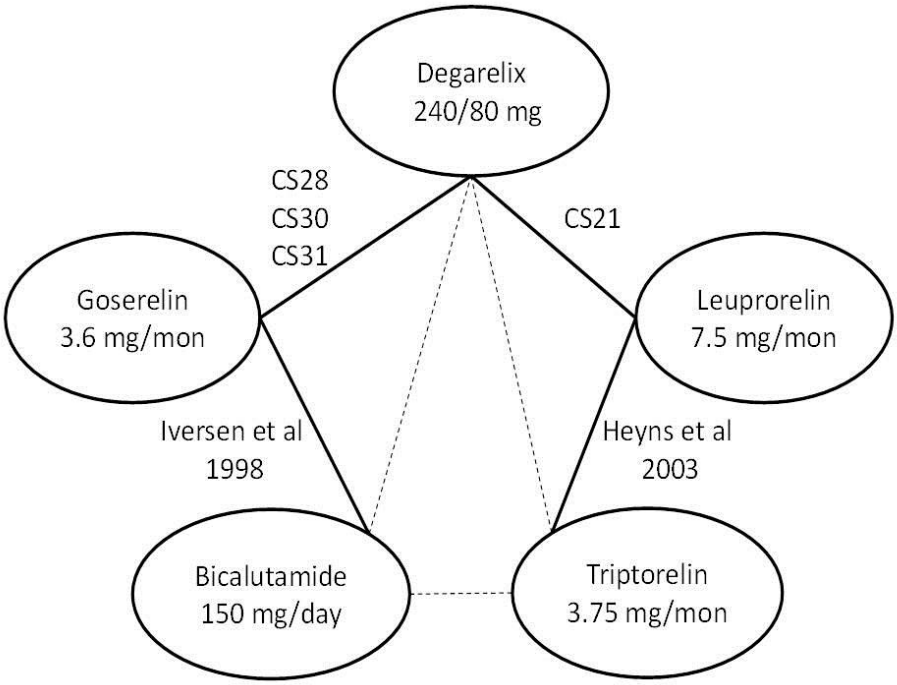
Study (n)	Interventions compared	Study participants	Outcome measures reported	Main conclusions	Reasons for inclusion in the MTC
CS21 CS28 CS30 CS31	Degarelix	Men with prostate cancer	As described in section 4.2		
Heyns *et al* (2003) (n=284)[124]	Triptorelin 3.75 mg Leuprorelin 7.5 mg	Men with advanced prostate cancer	Testosterone suppression Serum LH Bone pain Median PSA Survival Safety	Triptorelin reduced testosterone levels less rapidly but maintained castration as effectively as leuprorelin	Overall survival reported)
Iversen *et al* (1998) (n=480)[125]	Bicalutamide 100 mg Bicalutamide 150 mg Castration (surgical or goserelin 3.6 mg)	Patients with previously untreated non-metastatic (M0) advanced prostate cancer	Time to death Objective progression Treatment failure QoL Safety	Bicalutamide 150 mg provided similar survival outcome to castration, and improved QoL sexual interest and physical capacity	Most patients [86%] in the castration group received goserelin; overall survival reported)

Key: AE = adverse event; LH = luteinising hormone; LHRH = luteinising hormone-releasing hormone; MTC = mixed-treatment comparison; PSA = prostate-specific antigen; QoL = quality of life; UTI = urinary tract infection

The network of treatments included in the synthesis comparator set for the MTC of overall survival is shown in Figure 11. No direct head-to-head evidence for overall survival in degarelix versus bicalutamide or degarelix versus triptorelin was identified by the manufacturer.

As the decision problem limits the treatments in the synthesis comparator set to degarelix; goserelin; leuprorelin; triptorelin; and bicalutamide it was not possible to add other treatments, such as surgical castration to the synthesis set in order to make a connected network. The addition of surgical castration as a treatment in the synthesis comparator set would provide more data to inform the MTC.

Figure 11. Replicated from the MS (Figure 2; page 20) Network of trials used in mixed-treatment comparison – overall survival outcome



4.4 Summary and critique of submitted evidence in the MTC

4.4.1 Summary of submitted clinical evidence for the MTC

The Heyns (2003) study is reported to show that triptorelin reduced testosterone levels less rapidly but maintained castration as effectively as leuprorelin. The Iversen (1998) study is reported to show that bicalutamide 150 mg provided similar survival outcome to castration, and improved sexual interest and physical capacity. The MS states that PSA progression (recurrence/ failure) data were not available and so overall survival is the only outcome that is used in the MTC.

4.4.2 The manufacturer's approach to validity assessment for the MTC

Quality assessment was undertaken for the Heyns (2003) and Iversen (1998) studies and presented in appendix of the MS (MS pages 239/240). The Centre for Reviews and Dissemination (2008) template for quality assessment template is employed however the subsequent results and conclusion from the exercise are not discussed. Therefore there is no discussion of the risks of bias to which these two studies may be vulnerable to and

subsequently no adjustments were made to the MTC analysis on the basis of such identified biases.

The manufacturer states that *"Heterogeneity across the trials used in the MTC analysis could not be evaluated, as only a single trial was available for goserelin versus bicalutamide, as well as one for leuprorelin versus triptorelin"* (MS page 87). It is unclear why this reason would prevent the evaluation of heterogeneity. The ERG believes that a sensitivity analysis using an informative prior for the heterogeneity parameter should be performed

4.4.3 The statistical approach used within the MTC

The methods of the MTC are described on page 86 of the MS: *"Markov chain Monte Carlo methods in WinBUGS software (MRC Biostatistics Unit, Cambridge, UK) were used to conduct the random-effects MTCs. The WinBUGS code for Bayesian analysis is available from a report by Dias et al134 (see Appendix C for the WinBUGS code used). A non-informative or vague prior was used, and results were obtained by 200,000 iterations after a burn-in of 100,000."* The ERG considers that is not clear what method has been used to assess the convergence of the MCMC chains. The ERG believes that calculating the Gelman-Rubin convergence statistics is a preferred approach, but that given the number of iterations it is highly likely that convergence had occurred.

The MS focuses on goserelin in the base case despite the main pivotal CS21 trial of degarelix being versus leuprorelin. The MS states that *"Published evidence and results from systematic reviews indicate that none of the LHRH agonists has superior clinical efficacy over the others"* (MS page 21). Additionally the manufacturer assumes for the model that the efficacy and safety profiles of the alternative LHRH agonists are equal to leuprorelin 7.5 mg. However the ERG considers that the assumption that none of the LHRH agonists demonstrates superior clinical efficacy does not necessarily demonstrate clinical equivalence. The ERG requested the manufacturer to clarify how the non-significant difference in overall survival (page 86) between LHRH agonists in the MTC demonstrates equivalence in clinical efficacy and effectiveness.

The manufacturer responded that *"it is recognised that while the MTC provided does not conclusively demonstrate equivalence in clinical efficacy and effectiveness, the results from the MTC support the findings from previous systematic reviews and meta-analyses that none of the LHRH agonists exhibit superior clinical efficacy of effectiveness over another."*

The ERG has reviewed the two published sources of evidence referenced in the MS (page 86) in support of equivalent clinical effectiveness and efficacy of all LHRH agonists. Hemels *et*

al., (2002) was a poster, and the ERG considers that it is not appropriate to cite this reference since it has not been published in a peer reviewed journal. Seidenfeld et al (2000)[36] concluded that there was no evidence of difference in overall survival among the LHRH agonists, and the LHRH agonists included in the analysis were leuprolide, goserelin and buserelin. Triptorelin was not included in this paper. The study comparing triptorelin and leuprorelin (Heyns el al 2003) in the MTC was conducted after Seidenfeld et al (2000).[36] Hence, the results from Seidenfeld et al (2000)[36] need to be interpreted with caution.

The assumption that the absence of superiority from any of the LHRH agonists demonstrates clinical equivalence between the LHRH agonists is therefore acknowledged as incorrect but unjustly assumed in the MS.

4.4.4 The manufacturer's approach to outcome selection within the MTC

The MTC is limited to the overall survival outcome. The ERG considers that it may not be appropriate to compare these treatments solely on the basis of this outcome in the MTC because, as discussed previously, none of the trials are designed to detect differences in survival in this population. Outcomes which are more relevant to the response rate (either testosterone or PSA) are the focus of the clinical evidence submitted for degarelix and the primary endpoints of the RCTS for degarelix. Additionally whilst quality of life was measured in the Iversen (1998) study and across all degarelix trials it was not included as an outcome for assessment in the MTC.

The manufacturer conducts an MTC of overall survival between the treatments in the synthesis comparator set using odds ratios from different time points across the six included studies. After a request for clarification from the ERG, the manufacturer stated that the respective time points for death in the MTC were:

- Three months for CS28, CS30 and CS31
- 12 months for CS21
- Nine months for Heynes et al, 2003
- Four years for Iversen et al, 1998

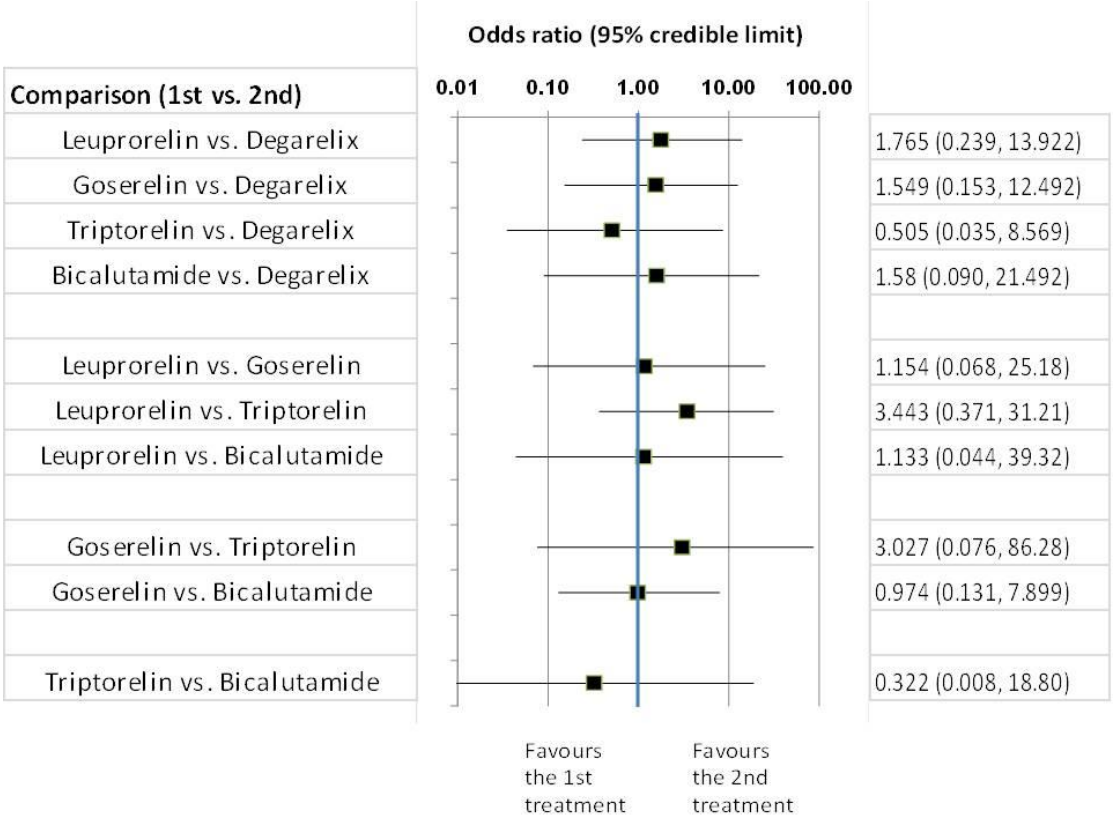
The assumptions behind this choice of analysis are not justified in the MS. The manufacturer stated that *"Although a HR of the overall survival is the most desirable outcome statistic, available data from the included RCTs were not sufficient and an OR was, therefore, used."* The ERG believes that given the time point where the number of events has been reported in

each study, a complimentary log-log model can be used to take into account different study durations and the treatment effect is measured by the hazard ratio in the model.

4.4.5 Results of the MTC

The results of the MTC for overall survival (MS page 87) are presented in Figure 12. This forest plot shows that the mortality when treating with triptorelin was lower than when treating with degarelix (odds ratio 0.505), but the difference was not statistically significant (95% CrI: 0.035, 8.569). Leuprorelin and goserelin were associated with increases in mortality compared to degarelix, but the effects were not statistically significant (odds ratio of leuprorelin vs. degarelix 1.765 95% CrI: 0.239, 13.922; odds ratio of goserelin vs. degarelix 1.549 95% CrI: 0.153, 12.492). The ERG considers that there is potential that the treatment effect of triptorelin on overall survival is different from the effects of leuprorelin and goserelin.

Figure 12. Results of mixed treatment comparison between degarelix and relevant comparators – death outcome (odds ratio [95% credible limit]) replicated from page 87 of the MS



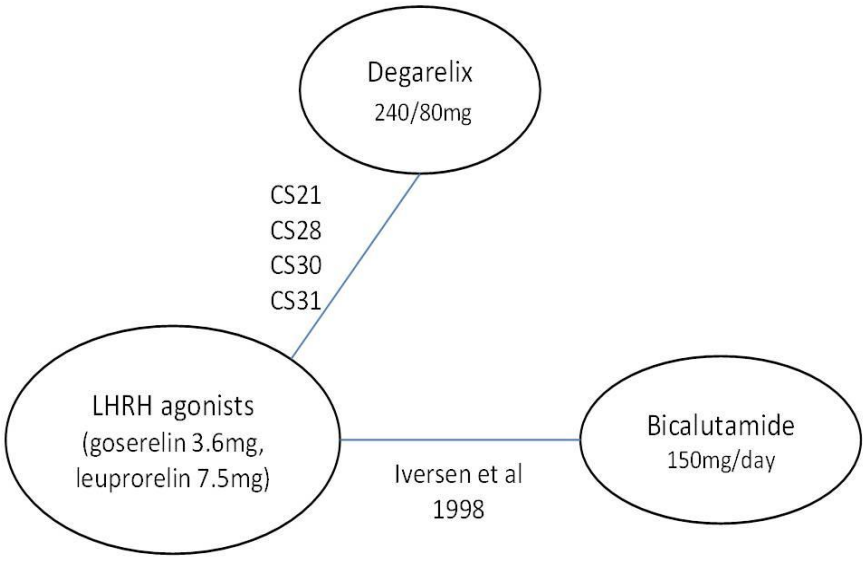
During the clarifications process, the ERG requested the manufacturer to provide the results of the MTC including bicalutamide as a comparator via a naïve indirect comparison with appropriate subgrouping from CS21 and for justification if it was not possible to do so. The

manufacturer responsed that *"bicalutamide monotherapy was included as a comparator in the MTC, as described on pages 81–88 in the submission. A naive indirect comparison for bicalutamide was not completed as it may provide misleading or biased estimates of treatment effects.1"*. As the baseline characteristics of the CS21 subgroup patients are not provided in the MS it is unclear how similar the population is to the trial populations reported in the Iversen *et al.,* (1998) study to assess suitability for a naïve indirect comparison.

The ERG also requested the manufacturer to provide the results of the MTC with all the luteinising hormone-releasing hormone (LHRH) agonists so that there were 3 groups within the MTC network: degarelix; LHRH agonists (including goserelin, leuprorelin and triptorelin); as well as bicalutamide monotherapy.

The manufacturers completed this request. They stated that the "three LHRH agonists (goserelin, leuprorelin and triptorelin) were considered as the same treatment. The study by Heyns et al (2003)2 could not be included in this MTC, as it compared different LHRH agonists (leuprorelin and triptorelin). The modified network of trials, in which three interventions were compared (degarelix, LHRH agonists and bicalutamide monotherapy), is shown below.

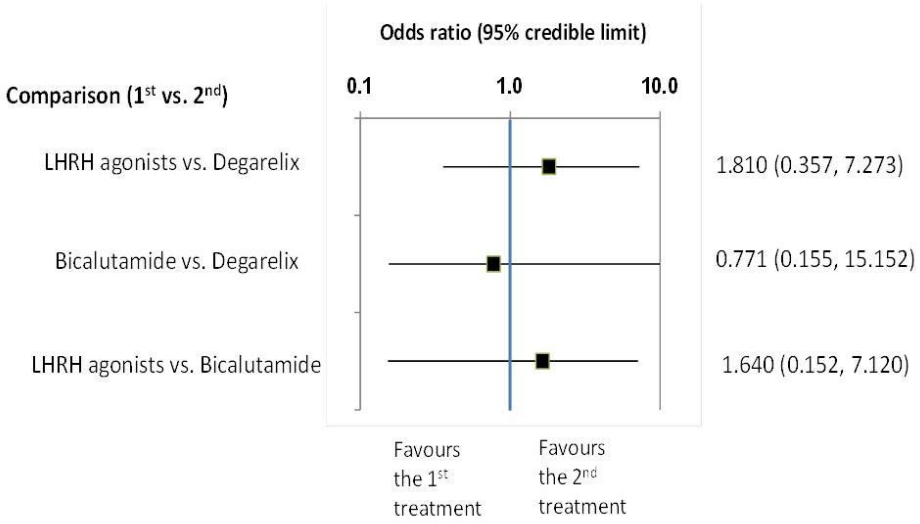
Figure 13. Modified MTC network provided by the manufacturer in the clarification process following ERG request



The results of the MTC are shown in the figure below. "*The differences between degarelix and LHRH agonists or bicalutamide monotherapy were not statistically significant (odds*

ratio [OR]=1.81; 95% credible limit [CL] 0.36 to 7.27 for comparing with LHRH agonists; and OR=0.77; 95% CL 0.16 to 15.15 for comparing with bicalutamide). The difference between LHRH agonists and bicalutamide was, similarly, non-significant."

Figure 14. Revised MTC between degarelix, LHRH agonists and bicalutamide – overall survival outcome (odds ratio) provided by the manufacturer in the clarification process



The ERG considers that it may not be appropriate to assume that all interventions in the LHRH agonists were identical. An alternative hierarchical model to take into account the class effect may be preferred.

The ERG also requested the manufacturer to provide the results of the MTC for all outcomes including adverse events in the MTC and for justification if this analysis was not possible. The manufacturer responded that "*Overall survival was a common outcome from studies included within the MTC. MTC was impossible for other efficacy and safety outcomes, as they were measured and reported very differently across trials. An exception was the rate of hot flushes, which can be used for MTC*". The results of this MTC indicated that there were no statistically significant differences in the hot flush rate between degarelix and comparators (see Table 24).

Table 24. Results of MTC of rates of hot flushes provided by the manufacturer during the clarifications process following ERG request

	Odds ratio	95% credible limits	
Leuprorelin vs. Degarelix	0.224	0.072	1.570
Goserelin vs. Degarelix	1.149	0.457	3.731
Triptorelin vs. Degarelix	0.229	0.057	3.861
Bicalutamide vs. Degarelix	0.145	0.038	1.603

Note: OR <1 indicates the first treatment was associated with fewer hot flushes compared with the second treatment

4.4.6 Additional clinical work conducted by the ERG

The WinBUGS code submitted by the manufacturer showed that informative priors were used for the treatment effects and baseline treatment effects. However, no justification has been given in the MS. The ERG considers that a possible explanation could be that there were no events in the control arm in two of the studies comparing goserelin and degarelix. Since no study ID has been provided in the WinBUGS code, the ERG is not able to identify the studies. There is also an issue of unidentifiable heterogeneity parameter in the manufacturer's MTC (see section 4.3.2 of this report). The ERG re-ran the model using an informative prior (half normal with mean 0 variance 0.32^2) for the heterogeneity parameter; and an informative prior (normal with mean 0 and variance 10) for the baseline treatment effect; but non-informative priors for the treatment effects. The results suggested that there was small heterogeneity between studies with the point estimate of the between study standard deviation being 0.21 and 95% CrI 0.01-0.71. Table 25 shows that triptorelin was associated with lower mortality than leuprorelin (odds ratio 0.2753 95% CrI: 0.06429, 0.9731).

Table 25: Mortality – Odds ratios and 95% credible intervals relative

Comparison	Odds Ratio (95% CrI)
Leuprorelin vs. Degarelix	1.84 (0.52, 6.75)
Goserelin vs. Degarelix	1.93 (0.18, 17.87)
Triptorelin vs. Degarelix	0.50 (0.07, 3.08)
Bicalutamide vs. Degarelix	2.02 (0.17, 20.9)
Goserelin vs. Leuprorelin	1.03 (0.07, 13.97)
Triptorelin vs. Leuprorelin	0.28 (0.06, 0.97)
Bicalutamide vs. Leuprorelin	1.08 (0.07, 16.21)
Triptorelin vs. Goserelin	0.26 (0.01, 5.04)
Bicalutamide vs. Goserelin	1.05 (0.49, 2.28)
Bicalutamide vs. Triptorelin	4.03 (0.19, 82.88)

The ERG believes that a model using odds ratios to analyse overall survival may not be appropriate (see section 4.3.4). After a request for clarification from the ERG, the manufacturer stated the time points for death in the studies included in the MTC (3 months for CS28, CS30 and CS31; 12 months for CS21; 9 months for Heyns et al, 2003,[37] 4 years for Iversen et al, 1998[10]). Using the given time points, the ERG performed an additional analysis, taking into account different study duration in the model. The conclusion supports the results from the model using odds ratios above (see Table 26).

Table 26: Mortality – Hazard ratios and 95% credible intervals relative

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)

4.5 Conclusions

The ERG is satisfied that all relevant RCTs were included in the clinical effectiveness review for degarelix and the manufacturer was forthcoming in providing clinical study reports and responding to the clarification requests.

As patients with localised and not classifiable prostate cancer were included in the six RCTs of degarelix, the trial population is not entirely reflective of the target population for which degarelix is indicated. For example, 50.3% of the main pivotal trial CS21 population had localised or not classifiable disease. The manufacturer uses of the higher risk (PSA >20 ng/ml) subgroup in the economic analysis, but the baseline characteristics and clinical efficacy results for this subgroup are not provided in the MS.

There is no clear evidence that treatment effect is not dependent on the stage of disease. The manufacturer claims that tests for an interaction between the disease state and treatment effect showed that treatment effect is not dependent on the stage of disease but the ERG could not find evidence substantiating this claim.

Flare protection was not consistently used in the trials for the LHRH comparators. A pooled analysis of degarelix versus LHRH plus anti-androgen flare protection should be interpreted with caution as the manufacturer compares the outcomes of 974 patients who received degarelix with 69 patients who received an LHRH agonist plus bicalutamide.

The manufacturer excluded trials CS35 and CS37 for some analyses on the basis of the unlicensed, intermittent dosing regimen but subsequently included trial CS35 for selected analyses without sufficient justification. Inappropriately pooled analyses, such as trials CS21 and CS35 which use different dosing regimens, for PSA response between degarelix versus LHRH plus flare protection resulted in a far less favourable PSA response rate for the comparator than the subgroup analyses from trial CS21 alone reported in the CSR. Conversely in instances when trial CS35 are less favourable to degarelix such as in testosterone response, this trial is omitted due to heterogeneity or lack of relevance to the decision problem. The ERG considers that trial CS35 should not have been included in any pooled analyses.

The manufacturer conducted simple pooled analyses instead of meta-analyses from the degarelix RCTs for testosterone response; PSA response; PSA PFS; s-ALP; LHRH agonist treatment plus flare protection subgroup and adverse events. Simple pooling ignores the characteristics of individual studies and relies on the assumption that there is no difference between individual studies which may yield counterintuitive or spurious results[21,23]. The

manufacturer makes the conclusion that degarelix is associated with statistically lower risks of fractures, joint-related signs and symptoms, and urinary tract-related adverse events than LHRH agonists however this is based on simple pooled analyses reported in two posters and an unpublished paper.

All the results from the meta-analysis need to be interpreted with caution. The included trials in two of the meta-analyses (IPSS and prostate size) only compared degarelix against goserelin and therefore the conclusion stated by the manufacturer about degarelix versus LHRH agonists is too broad. Additionally the meta-analysis of overall survival and PSA response only compare against leuprorelin or goserelin and therefore conclusions about all LHRH agonists cannot be drawn. The manufacturer includes different treatments in a pairwise meta-analysis which should be avoided unless there is evidence that the two drugs (leuprorelin and goserelin) produce identical treatment effects. Statistically significant heterogeneity was reported for the PSA response meta-analysis and no formal meta-regression was performed to justify this.

The manufacturer inappropriately used the conclusions from two previously conducted meta-analyses as evidence that none of the LHRH agonist have clinical superiority. Triptorelin was not included in the references cited by the manufacturers and one of the references was a poster and so should not be cited. The results from the manufacturer's MTC suggested that there is potential that the treatment effect of triptorelin on overall survival is different from the effects of leuprorelin and goserelin but this potential difference was not explored in the MS. Instead the manufacturer claimed that the results supported the previous paper and poster which did not include triptorelin. Additionally the manufacturer uses odds ratios of mortality from the included studies which vary in duration from 3 months to 4 years. This assumes that the rate of death is constant between trials for MTC on survival, despite the different time points. The ERG's revised analysis shows that triptorelin was associated with lower mortality than leuprorelin. Whilst clinical advice to the ERG was that selection of LHRH agonists in clinical practice is frequently determined by cost, it is the ERG's opinion that there is not sufficient evidence that the LHRH agonists are equivalent in clinical effectiveness.

Conclusions are drawn about clinical equivalence from a meta-analysis which is based on the overall survival only. None of the included studies were designed to capture meaningful differences in survival. This is reflected in the low number of deaths in the trials.

5 ECONOMIC EVALUATION

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

5.1.1 Methods of cost effectiveness review

A systematic search and review was conducted to identify cost-effectiveness studies for advanced prostate cancer patients treated with LHRH agonists. A comprehensive search strategy was utilised, incorporating terms for degarelix and its comparators, together with terms for prostate cancer and an economics filter, which were taken from the Centre for Reviews and Dissemination (CRD) website. The manufacturer reported searching 6 databases (Medline and Medline in Process, Embase, Cochrane Library, CINAHL, EconLit and Web of Science) for cost-effectiveness studies. However, only the Medline strategy was provided in Appendix 10, 12 and 13 of the MS (page 246, 250 and 253, respectively). By contrast to the clinical effectiveness searches for degarelix; comparators and; adverse events, the ERG did not attempt to translate or replicate the search strategy.

In addition to the cost effectiveness search the MS also includes two further searches:

- Measurement and valuation of health effects search (section 7.4)
- Resource identification, measurement and valuation (section 7.5)

The ERG considered that the sources searched and strategies were comprehensive. Furthermore, the updated searches (Appendix 3) in September 13th 2013 by the ERG did not identify new studies that have been published since the searches were carried out by the manufacturer in April 2013.

5.1.2 Inclusion/exclusion criteria used in the study selection

The key inclusion criteria for the search are described in Table 27 below.

Table 27 Eligibility criteria and rationale for each criterion (MS page 106; Table 20)

Inclusion Criteria		
Category	**Inclusion Criteria**	**Rationale**
Population	Adults with advanced hormone-dependent prostate cancer (locally advanced or metastatic, including biochemical relapse) in whom orchidectomy is not preferred	This was the population identified by the NICE final scope and is in accordance with the licensed indication for degarelix.
Study type	Full economic evaluation (including cost-consequence, cost-minimisation, cost-effectiveness, cost-utility and cost-benefit evaluations) that compares two or more interventions	The aim of the review was to identify relevant economic evaluations
Outcomes	Incremental costs and QALYs; any other measure of effectiveness reported together with costs	The aim of the review was to identify relevant economic evaluations, which must report costs
Interventions	The intervention of interest was degarelix (see Appendix 10 for the terms used to filter by this agent)	
Comparators	The comparators included in the search included gonadotrophin hormone agonists and androgen antagonists (see Appendix 10 for a full list of terms)	The comparators for the literature review were selected in accordance with the final NICE scope
Other	Studies must provide sufficient detail regarding methods and results to enable the methodological quality of the study to be assessed, and the study's data and results must be extractable	Only studies which provided extractable data and results were usable

Exclusion criteria		
Category	**Exclusion Criteria**	**Rationale**
Publication Type	Letters; editorials; reviews of economic evaluations (although reference lists of these were hand-searched)	Primary study articles were required.

5.1.3 Studies included in the cost effectiveness review

The review identified three studies which are described in Table 28 below.

Table 28 Summary list of other cost-effectiveness evaluations (MS page 109; Table 21)

Study	Year	Country	Patient age	QALYs	Costs	ICER (per QALY gained)
Lu et al[38]	2011	UK	70 years old	Degarelix: 2.45 Triptorelin + AA: 2.44	Degarelix: £3,883 Triptorelin + AA: £3,125	£59,012
Lee et al[39]	2012	UK	Not stated	ITT population Degarelix: 3.77 Leuprorelin + AA: 3.53 PSA >20 ng/ml population Degarelix: 3.55 Leuprorelin + AA: 3.28	ITT population Degarelix: £19,440 Leuprorelin AA: £24,59 PSA >20 ng/ml population Degarelix: £24,621 Leuprorelin AA: £30,43	ITT population Degarelix is dominant PSA >20 ng/ml population Degarelix is dominant
Hatoum et al[40]	2013	USA	72 years old	Degarelix: 4.20 Leuprorelin +AA: 3.46	Degarelix: $37,174 Leuprorelin +AA: $36,9	$245

Model Summaries:

Lu et al *[38]Decision tree and Markov model to evaluate cost-effectiveness of monthly degarelix vs 3-monthly triptorelin plus short-term anti-androgen treatment within a metastatic population (the title states advanced, however, the paper only covers metastatic patients). Time-horizon of 10 years. The decision tree monitored patients from the start of hormonal treatment to the end of Month 1. During this time, patients either: developed severe SCC, developed mild symptomatic SCC, experience BOO or had no complications. After treatment, they entered the Markov model, which consisted of 3 stages: in response, progressive disease and death. A monthly cycle was assumed.*

Lee et al *[39]Markov model including treatment sequencing comparing the cost effectiveness of first line treatment with degarelix compared to leuprorelin.*
The primary efficacy variable was time to PSA progression (recurrence/failure). The adverse events of SCC and MSE were also included.

Hatoum et al *[40,41]20-year time horizon semi-Markov model. Costs and QALYs discounted at 3%. Compared monthly degarelix 240/80 with monthly leuprolide 7.5 mg. as first-line*

treatment of locally-advanced prostate cancer. Patients entered the model when receiving either degarelix or leuprorelin and were then subjected to monthly probabilities of PSA progression or death. A patient transitioned to second-line or a subsequent line of ADT treatments when PSA recurred. Once a patient reached the stages of either 'passive monitoring', 'chemotherapy' or 'palliative care', the patient's utility was then considered to be further reduced since prostate cancer had reached the hormone-resistant stage. [MS Table 21]

5.1.4 Critique of the conclusions from the cost effectiveness review

The MS review included the following conclusion. "*the studies as a whole are inadequate to fully inform decision-making in the UK context. The primary limitation of the study by Hatoum et al[40] is that it takes a US payer's perspective; as such, the costs incorporated may not be appropriate for the UK. The study by Lu et al[38] is limited in that its model structure does not account for all of the additional benefits of treatment with degarelix; the result is that the cost-effectiveness of degarelix is likely to be underestimated. The model reported by Lee et al[39] appears to be promising, but as it was only available as a poster, there is a lack of detail on the reported method (as shown by the checklist in Appendix 11 in Section 10.11). Additionally, while a couple of scenario analyses are reported, the analysis of uncertainty is insufficient to fully inform the decision-making problem. Hence, a de novo economic evaluation of degarelix has been performed.*" [MS page 111]

The ERG would agree that no published cost-effectiveness analyses meeting the NICE Reference Case were identified and therefore a *de novo* economic evaluation was warranted.

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

5.2.1 NICE Reference Case checklist

Table 29 below presents a comparison of the MS with the NICE Reference Case.

Table 29: Comparison of MS with the NICE Reference Case checklist

Element of health technology assessment	Reference Case	Does the submission adequately address the Reference Case?
Defining the decision problem	The scope developed by the Institute	Yes
Comparator	Therapies routinely used in the NHS, including technologies regarded as current best practice	Bicalutamide monotherapy not included as a comparator
Perspective on costs	NHS and PSS	Yes
Perspective on outcomes	All health effects on individuals	Yes
Type of economic evaluation	Cost-effectiveness analysis	Yes
Synthesis of evidence on outcomes	Based on a systematic review	Yes
Measure of health effects	QALYs	Yes
Source of data for measurement of HRQL	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes

5.2.2 Model structure

The manufacturer's model has a Markov-treatment sequence structure and assumes that all patients follow an identical treatment pathway. The model health states mirror the treatment pathway assumed for patients in the UK with advanced hormone-dependent prostate cancer (MS page 113; Figure 19). All patients receive treatment with degarelix/LHRH agonists. Following PSA progression the anti-androgen bicalutamide will be added followed by a period of anti-androgen withdrawal. Following the end of response to anti-androgen withdrawal treatment with degarelix/LHRH agonists will stop and all patients receive chemotherapy, then abiraterone, then supportive care and lastly palliative care. The model assumes that all patients receive each line of treatment line if they are still alive. A scenario

analysis assumes that treatment with degarelix/LHRH agonists continues until death in addition to the later lines of treatment.

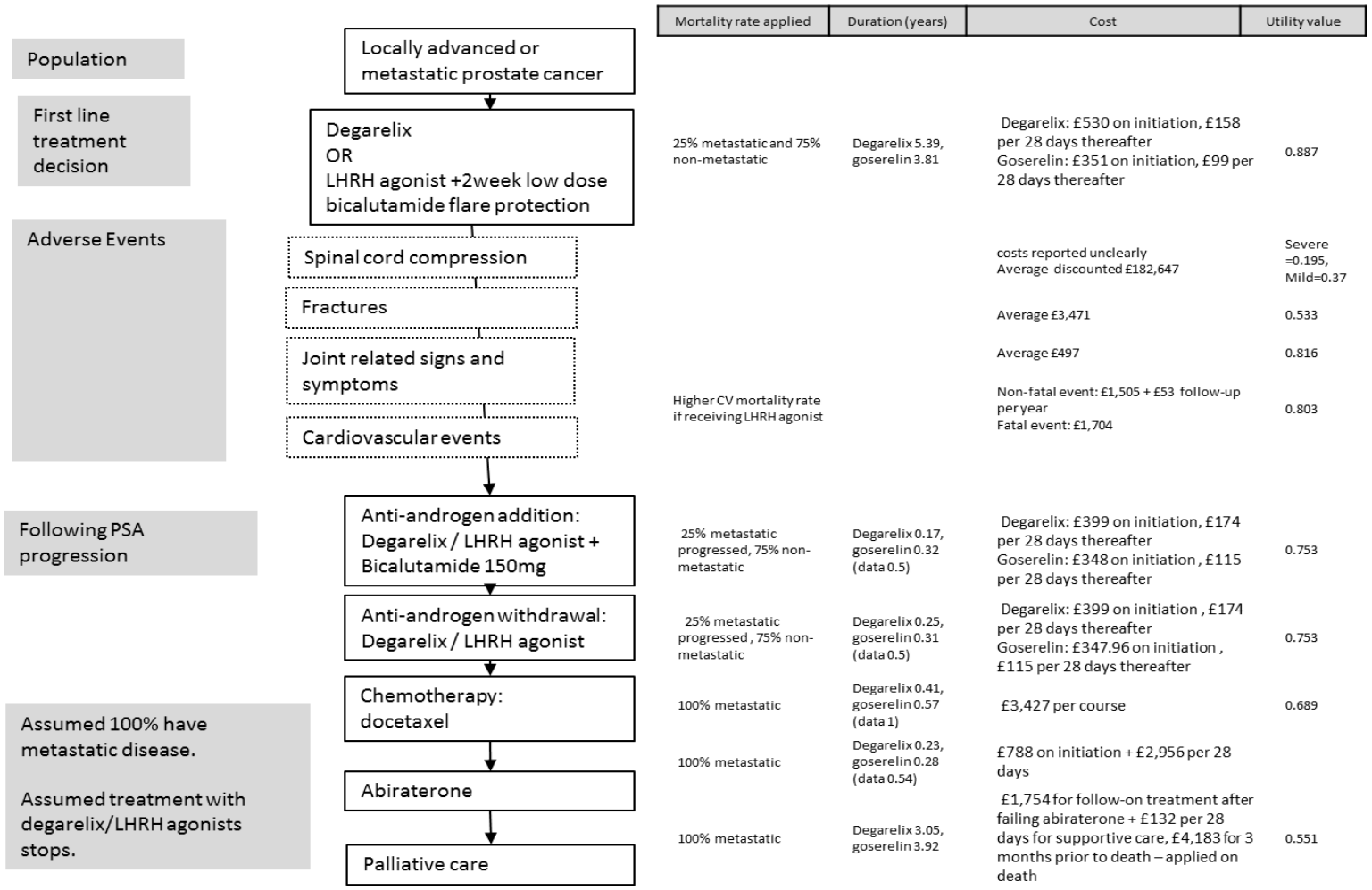
As the disease progresses, patients move through the pathway. The HRQoL associated with each disease state either falls or remains constant as patients progress. The model states also capture the treatment costs; administration costs; and monitoring costs associated with each of the treatments in the pathway. The adverse events experienced whilst on the different treatments further influence costs, patient HRQoL and, in the case of cardiovascular events, mortality.

Transition from first-line treatment is based on data on PSA progression on degarelix/LHRH agonists. The duration of response to subsequent lines of treatment (time spent in subsequent health states) is based on estimated response durations reported in the EAU guidelines. Mortality rates, which are age specific and dependent on the presence/absence of metastatic disease, were derived from ONS data and Scottish prostate cancer mortality data. Mortality for patients on first line-treatment was calculated based on the proportions of patients with localised, locally–advanced and metastatic disease from the CS21 trial. Patients in the health states: chemotherapy; abiraterone; and supportive/palliative care were assumed to have metastatic disease so this mortality rate was applied. However, a different mortality rate was applied for patients receiving abiraterone. An increased hazard of mortality was applied for patients with metastatic disease once they had progressed from first-line treatment.

ERG critique

An ERG representation of the model structure which describes key assumptions is presented in Figure 15.

Figure 15: ERG representation of model structure



The Markov treatment sequence structure of the model assumes an identical treatment sequence for all patients and estimates disease stage based on location in the treatment sequence. Clinical advice received by the ERG indicates that there is variation in the treatment sequence between patients, so this model structure is unlikely to be appropriate across the whole patient population. The ERG considers that a model structure that explicitly models time to metastatic disease and time to death whilst also allowing variation in treatment sequences would be more appropriate, flexible and transparent. For example, it is assumed that all patients commencing treatment for locally advanced prostate cancer would move to the metastatic disease state at the end of anti-androgen withdrawal response. It is not clear that this assumption is clinically realistic.

Clinical advice received by the ERG suggests that the pathway assumed within the MS (Figure 1 of this report) is significantly different to clinical practice. An alternative treatment pathway is suggested in Figure 2 (section 2.2) of this report. Differences highlighted by the clinical advice include:

- It is usual for treatment with degarelix/LHRH agonists to be continued to be administered until death (the MS assumes that treatment with degarelix/LHRH agonists will stop when treatment with chemotherapy commences).
- A proportion of patients undergoing radical local treatment with surgery or radiotherapy will fail and then normally receive hormone based treatment at some later point in time.
- Around 30%-70% of advanced prostate cancer patients receive chemotherapy.
- Not all patients receive abiraterone as it has limited efficacy in poor performance patients (ECOG Performance status 2 or more).
- Abiraterone is only licensed for use following chemotherapy however it can be used before chemotherapy via the cancer drugs fund.
- The competitive blocker enzalutamide is also used.
- Watchful waiting in the elderly can be used.

The MS states that "*In line with the [*Summary of product characteristics *] SPC, in the base case model, patients are treated with degarelix or one of the comparator treatments until their condition is no longer defined as being hormone-dependent. At this stage, their condition has progressed beyond the licensed indication of degarelix and the other comparator treatments. In the model, patients are considered as no longer having hormone-dependent prostate cancer once they receive chemotherapy.*" "*Patients can receive LHRH agonists or degarelix, even if the disease becomes hormone refractory. The impact of this*

treatment practice is tested within scenario analyses." The SPC states that "*FIRMAGON is a gonadotrophin releasing hormone (GnRH) antagonist indicated for treatment of adult male patients with advanced hormone-dependent prostate cancer.*" The SPC does not mention stopping treatment when disease becomes hormone refractory. The ERG believes the SPC specifies that patients must be hormone-dependent to start treatment but has no recommendations with regard to stopping treatment. Clinical advice received by the ERG states that treatment with LHRH agonists or degarelix would continue until death and this assumption is used in the ERG base case.

The approach used to model of mortality in the manufacturer's model was not transparent or clear to follow. The approach to survival modelling applied a different mortality rate for patients receiving abiraterone. The ERG believes that this is likely to be appropriate only if the Scottish registry data population which informs relative survival did not include patients who received abiraterone. As abiraterone only received a European licence in September 2011, this may well be the case.

5.2.3 Population

The population consists of adult male patients aged 72 with advanced hormone-dependent prostate cancer. The base case analysis reflects the ITT population from the CS21 and CS21A trials**.** The model based the proportion with metastatic disease on that seen in the CS21 trial where 20% were metastatic and 19% unclassified (MS Table 29). Table 30 summarises the data and model information provided for each of the subgroups included within the NICE scope.

Table 30 Summary of information presented within the MS on subgroups included within the NICE scope

Subgroup	Information provided in MS [MS clarification D3]
Patients with PSA levels >20ng/ml	Subgroup analysis undertaken using efficacy data from CS21 undertaken
Patients with spinal metastases with impending or actual SCC	Data not collected in clinical trials
Patients with high tumour volume with impending or actual urinary outflow obstruction	The only trial with data was CS28 for which the subgroup n=42
Patients with bony metastases associated with intractable pain	Data not collected in clinical trials
Patients for whom standard anti-androgen treatment is contraindicated	Data not collected in clinical trials
Patients at risk of evolving cardiovascular comorbidity	Analysis for 'patients with baseline cardiovascular disease' undertaken assuming PSA progression efficacy for subgroup is equal to that for whole population

ERG critique

The population considered in the manufacturer's economic analysis is appropriate. The MS stated that there was insufficient evidence available to consider cost effectiveness of all but two of the subgroups included within the final NICE scope. However, the ERG suggests despite the lack of evidence, it may have been worthwhile to consider subgroups in exploratory analyses. For example, clinical advice received by the ERG suggests that there may be considerable additional benefit in avoiding flare and associated adverse events in the subgroups of patients with spinal metastases with impending or actual spinal cord compression, and in patients with high tumour volume with impending or actual urinary outflow obstruction.

5.2.4 Interventions and comparators

The economic model compares treatment with degarelix to treatment with goserelin 10.8mg (Zoladex) in the base case. Comparisons of degarelix with goserelin (Novgos) and triptorelin (Gonapeptyl) are also included as scenario analyses. The MS states that bicalutamide monotherapy was not included as a comparator as: (1) bicalutamide monotherapy is indicated in a smaller patient population that includes only those with locally advanced, non-metastatic

prostate cancer, and (2) RCT evidence comparing it to degarelix and/or LHRH agonists was lacking.

ERG critique

A comparison with all LHRH agonists should be included. The cheapest comparator, goserelin (Novgos), is listed in the October 2013 British National Formulary (BNF) however it is not commonly used by clinicians in England and Wales (<0.1% in 2012 reported in D18 of clarification response) and when the ERG contacted the manufacturer Genus they stated it is no longer in production.[42] Hence, the ERG recommends that Novgos be excluded from the economic analysis. For leuprorelin (Prostap) and triporelin (Decapeptyl), the 1- and 3-monthly doses have equivalent costs however for goserelin (Zoladex) the 3-monthly dose is more expensive. For triporelin, the 6-monthly dose is the least expensive. Clinical advice received by the ERG suggests that a 3-monthly regimen may be preferred for convenience. The usage data in the MS (Table 6) suggests that both 1-monthly (3.75mg) and 3-monthly (11.25mg) versions of the LHRH agonists are used but that a 6-monthly (22.5mg) regimen is rarely used. The ERG notes that the usage data provided in the MS should be used with caution as goserelin is also used to treat other conditions such as breast cancer thus the data may not be representative for prostate cancer. Overall, the ERG suggests that both 1-monthly, 3-monthly and 6-monthly versions should be included within the economic analysis with the base case considering the least expensive regimens.

Bicalutamide monotherapy is a comparator included within the final scope of the appraisal. Clinical advice received by the ERG indicates that bicalutamide monotherapy is used for some patients with locally advanced prostate cancer (M0). Bicalutamide monotherapy may be used rather than LHRH agonists as it has fewer adverse events (for example in males in their 50s or 60s as it preserves testosterone, or in patients with existing bone conditions). It is also more convenient as it is administered as a tablet rather than an injection. The ERG considers that although the MTC network does not include any RCTs that directly compare degarelix with bicalutamide monotherapy, it does allow an indirect estimate to be generated. Evidence on the efficacy of bicalutamide monotherapy compared to goserelin was available from a study reported by Iversen. [10]

A bicalutamide monotherapy dose of 150mg has a monthly price of £6.73 (BNF) or £4.20 (eMIT) so is considerably less expensive than LHRH agonists or degarelix. The ERG believes that bicalutamide monotherapy should be included as a comparator for the locally advanced

subgroup. The ERG was unable to undertake an analysis which incorporated this comparator due to the model structure used.

5.2.5 Perspective, time horizon and discounting

The model takes a NHS and PSS perspective with a time horizon of 30 years and a discount rate of 3.5% applied to both costs and QALYs.

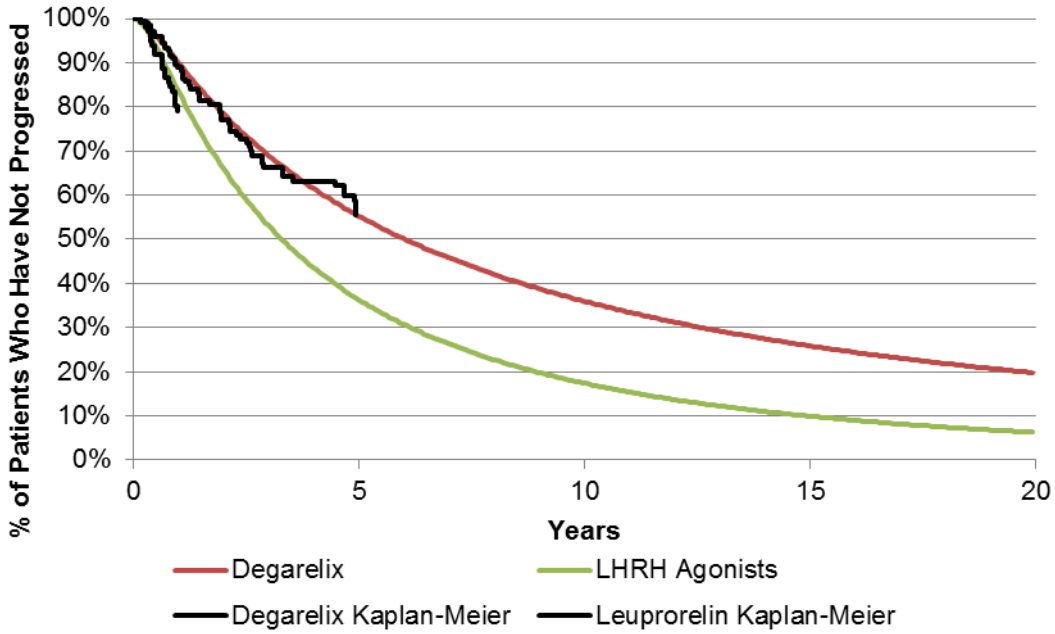
ERG critique

The perspective, time horizon and discounting are appropriate and are in line with the NICE Reference Case. Given a starting age of 72 years, 99% of patients are dead by the end of the time horizon.

5.2.6 Treatment effectiveness

The MS argues that each of the LHRH agonists have equivalent efficacy. The MS estimates efficacy data based on the CS21 and CS21A clinical trials which compare degarelix to leuprorelin for a period of one year before crossover was allowed. A hazard ratio for PSA progression of 1.71 (1.74) for leuprorelin compared to degarelix for the ITT population (PSA>20ng/ml population) was estimated from the CS21 and CS21A trial data. PSA progression on degarelix was modelled via a log-normal distribution which provided the best fit (lowest Akaike Information Criterion [AIC] score) of the five parametric curves considered (Weibull, log-logistic, log-normal, Gompertz and exponential). The PSA progression-free survival data and the fitted log-normal curves are shown in Figure 16. The hazard ratios were applied to the parametric curve fits assuming proportional hazards. Two scenario analyses were also presented: (1) the efficacy of degarelix and LHRH agonists were assumed equal; and (2) the efficacy of degarelix and LHRH agonists were assumed equal after 1 year.

Figure 16: PSA progression free survival data Kaplan-Meier curves and the fitted lognormal curves



The MS includes an MTC and presents estimates of odds ratios for overall survival. Other outcomes were not included within the MTC. The evidence network used within the MTC does not include any RCTs that directly compare degarelix with bicalutamide monotherapy. An indirect estimate for bicalutamide monotherapy was not presented. Results of the MTC were not used within the *de novo* economic model.

Efficacy data from a pooled analysis of five RCTs are presented in Section 6.5 of the MS. This includes ORs for death and the difference in death rate but does not include PSA progression. This section does not report the time point for this overall survival comparison and the trials were of lengths varying from 3 months to 12 months.

PSA progression was used as a surrogate outcome for overall survival; this is supported by a study by Hussain *et al.*, (2009)[43] which concludes that '*PSA-P, defined as an increase of 25% greater than the nadir and an absolute increase of at least 2 or 5 ng/mL, predicts OS in HSPC and CRPC and may be a suitable end point for phase II studies in these settings'*. The model assumes that after anti-androgen withdrawal 100% of patients will have metastatic disease which is associated with a higher mortality rate than non-metastatic disease. Hence, when degarelix and LHRH agonists are assumed to have differential efficacy in terms of PSA progression, the model structure results in a different overall survival predictions.

The manufacturer's model assumptions relating to treatment efficacy are described in Table 31.

Table 31: Modelling assumptions relating to treatment efficacy [Part of MS Table 33]

Assumption	Justification
Differential efficacy continues after the trial	The Kaplan–Meier Curves from CS21 show no indication of moving towards convergence. Sensitivity of the model to this assumption is tested in a scenario analysis
The efficacy across the doses of LHRH agonists is equal	The clinical literature available shows no statistically significant clinical difference between leuprorelin 3.75 mg and leuprorelin 7.5 mg. It therefore seems valid to assume that for leuprorelin there is no clinical difference between the doses.
The efficacy of goserelin and triptorelin, are equal to leuprorelin	The MTC reported in Section 6.7 and meta-analyses undertaken by Seidenfeld *et al*[36] and Hemels *et al* indicate that there is no significant difference in progression or mortality-related outcomes for patients on a variety of LHRH agonist.
The efficacy of an LHRH in combination with anti-androgen flare cover is equal to the efficacy of treatment with LHRH alone.	This test could only be undertaken on a small number of patients, as anti-androgens are provided only for flare cover it is not clinically likely that PSA progression is affected by its provision. Additionally, Oh *et al*[44] conducted an analysis of 1,566 patients, which concluded that anti-androgen therapy before LHRH agonists in metastatic prostate cancer was not associated with differences in fractures, SCC, BOO, or narcotic prescriptions. The trial data not only supports the equivalency of the efficacy between those patients receiving anti-androgen flare cover and those who do not; it also supports that degarelix has enhanced efficacy versus those who have flare cover as well as the population that predominantly does not (CS21). Pooled analysis from CS21 and CS35 degarelix trials showed that the PSA PFS failure rate (adjusted for baseline PSA, PCa stage and Gleason score) was significantly lower with degarelix than with LHRH agonists + anti-androgen flare protection for all patients (HR=0.490, p=0.0028); and that patients receiving LHRH agonists + anti-androgen flare protection still experienced testosterone surge.
Metastatic patients who progress from first-line treatment have an increased risk of mortality	This assumption is supported by the evidence reported in Hussain *et al.*[43] Sensitivity of the model to this assumption is tested in a scenario analysis.
Treatment pathway & stopping rule	Supported by the licensed indication. A scenario analysis is undertaken where patients remain on degarelix and LHRH agonists until death as certain clinical experts suggested this occurred as regular practice.

Key: BOO = bladder outlet obstruction; HR = hazard ratio; HRQL = health-related quality of life; LHRH = luteinising hormone-releasing hormone; MSEs = musculoskeletal events; MTC = mixed treatment comparison; PFS = progression-free survival; PSA = prostate-specific antigen; SCC = spinal cord compression

ERG critique

Equivalence of LHRH agonists:

The ERG believes that the assumption that all LHRH agonists have equivalent efficacy is unjustified. The MS states that this assumption is justified based on evidence from Seidenfeld *et al* (2000)[36] however this study does not include triptorelin. The ERG believes that it would be more appropriate to model the effects of each LHRH agonist individually. The ERG believes that rather than restricting to a single trial, the economic analysis should incorporate all relevant trial evidence.

Duration of effect on PSA progression:

The clinical trial data demonstrate a difference in PSA progression rates between degarelix and leuprorelin for a period of 1 year. It is unknown whether a differing PSA progression rate would be likely to continue after one year or if the difference could just be related to the low levels of flare protection administered in the trial. Clinical advice received by the ERG suggests that it is possible that the Kaplan Meier curves for PSA progression could meet again at a time point later than one year. Hence, the ERG believe that the scenario analysis presented in the MS in which the efficacy of degarelix and LHRH agonists were assumed equal after 1 year is most appropriate.

Relationship between PSA and overall survival:

Although the MS presents information on overall survival, the short duration of the clinical trials makes them inappropriate for demonstrating a difference in overall survival. Clinical advice received by the ERG suggests that it is not clear that degarelix offers an overall survival benefit compared to LHRH agonists. The ERG believes that the relationship between PSA progression and overall survival assumed within the MS is associated with uncertainty. For example, in contrast to the evidence reported by Hussain *et al*.,[43], clinical advice received by the ERG stated that "*PSA in this setting is flawed as a universal predictor of mortality*". A study by Scher *et al.,* (2013)[45] suggests PSA progression is inappropriate as a surrogate endpoint[29,45] The ERG recommends an analysis in which degarelix impacts on PSA progression but not on overall survival. Such an analysis is not presented in the MS and was not undertaken by the ERG due to the limitations of the model structure. However, the ERG did undertake an analysis in which the risk of mortality in metastatic patients is not influenced by progression from first-line treatment.

5.2.7 Health related quality of life

HRQL data were available from the CS21 clinical trial. Data were collected using the SF-12 v2 and the EORTC QLQ-C30 and these were each mapped to EQ-5D. The MS compared the results of four mappings and concluded that they all provide broadly similar results.

'The SF-12 v2 algorithm, however, provides consistently lower results than the algorithms based on the EORTC QLQ-C30.PSA progression has a significant effect on quality of life ($p<0.001$ using all mapping algorithms). When a patient progresses the utility value drops by approximately 0.1, which is consistent with the available literature.

The effect of treatment on utility differs when using the two algorithms. When using the Kontodimopoulos algorithm, the difference between the two treatment arms is not significant ($p=0.27$); however, the difference is significant when using the McKenzie and van der Pol algorithm ($p=0.03$), with utility being higher for patients on degarelix.

Of the AEs tested, fractures influence utility the most, with a drop in utility of 0.358 and 0.374, followed by cardiovascular events, with a drop of 0.090 and 0.117 for the Kontodimopoulos and McKenzie and van der Pol algorithms, respectively. The HRQL effects of JSS (0.064 and 0.082) are lower.'[MS p154]

Results from the Kontodimopulos mapping were incorporated into the model base case. A systematic search of HRQL data was undertaken. The effects of using alternative sources for utilities derived from this search were explored in the MS scenario analyses. A summary of the QoL values used in the cost-effectiveness analysis is shown in Table 32.

Table 32. Summary of quality-of-life values for cost-effectiveness analysis replicated from MS Table 41

State	Utility value	Confidence interval	Reference in submission	Justification
First-line treatment	0.887	(0.879–0.894)	7.4.4	Mapping algorithm produces an EQ-5D based utility in line with the reference case
Anti-androgen addition	0.753	(0.697–0.806)	7.4.4	Mapping algorithm produces an EQ-5D based utility in line with the reference case
Anti-androgen withdrawal	0.753	(0.697–0.806)	7.4.4	Assumed the same as for anti-androgen addition based upon Bayoumi *et al*[166]
First-line chemotherapy	0.689	(0.686–0.692)	7.4.5	Study using the EQ-5D identified using the literature search. Study by Bahl *et al*[164] chosen as included UK patients and had a large number of patients.
Palliative care	0.551	(0.527–0.580)	7.4.5	Study using the EQ-5D identified using the literature search. Study by Sanbolm *et al*[172] chosen as included European patients.
*Adverse events**				
Severe SCC	0.195	(0–0.390)	7.4.8	Used by Lu *et al*[144] in earlier analysis
Mild SCC	0.370	(0.270–0.470)	7.4.8	Used by Lu *et al* in earlier analysis
Fracture	0.533	(0.19–0.88)	7.4.4	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)	7.4.4	Mapping algorithm produces an EQ-5D based utility in line with the reference case
Non-fatal CV event	0.803	(0.66–0.94)	7.4.4	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 = SCC
* 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))

Table 33: Model assumptions relating to utility data (Part of MS Table 33)

Assumption	Justification
Patients who initially have severe SCC who improve have the same utility as those who have mild SCC	The publication by Lu *et al* only gave utilities for three SCC outcomes (cured, ambulant or non-ambulant).[144] The most reasonable assumption seemed to be that those who were improved from severe SCC but not cured had the same utility as those who were ambulant (mild SCC). This assumption is likely to favour the LHRH agonists rather than Degarelix as the risk of SCC is associated with treatment with LHRH agonists – reducing the disutility associated with SCC therefore reduces the benefit of treatment with degarelix. A scenario analysis is undertaken where SCC, fractures and joint-related signs and symptoms are not included in the model.
Patients who have a non-fatal cardiovascular event do not experience additional disutility from 28 days after the event	This assumption was incorporated to avoid undue complexity in the model. It is conservative from the perspective of the cost effectiveness of degarelix because the trial data indicate that patients treated with degarelix experience fewer non-fatal cardiovascular events. A scenario analysis is undertaken where the costs, mortality and disutility associated from fatal and non-fatal cardiovascular events are not included.
Rates of adverse events (MSEs and cardiovascular events) are not dependent on the dose of degarelix given	This assumption is supported by the data from the six pooled trials. Adverse events were only incorporated when there was a statistically significant difference in their distribution between patients on degarelix and those on leuprorelin and when they were not dose dependent. Some MSEs were excluded due to evidence of dose dependency – these events happened less frequently in those patients treated with degarelix so the exclusion of these events is conservative. A scenario analysis is undertaken where the cost and HRQL implications of SCC, fractures and joint-related signs and symptoms are not incorporated into the cost-effectiveness calculation.

ERG critique

The ERG believes that the scenario analyses using alternative sources for utilities derived from the systematic review were adequate to represent the uncertainty associated with utility values.

Safety

The economic model includes the following adverse events: fractures; joint-related signs and symptoms; cardiovascular events and; spinal cord compression (SCC). With the exception of SCC adverse event rates were modelled via Weibull curves fitted to pooled observations from six clinical trials. The Weibull models extrapolated the one year trial data. The MS assumes that the risk of adverse events is the same for each of the LHRH agonists. The pooled observations show a higher risk of each of these four adverse events for LHRH agonists compared with degarelix. The fitted Weibull curves result in the risk of adverse events

increasing over time for cardiovascular events and decreasing over time for joint related signs and symptoms. For fractures the Weibull model used indicated that the risk of adverse events would decrease over time for degarelix but increase for LHRH agonists. It was assumed that SCC did not occur with degarelix due to the absence of testosterone flare. For LHRH agonists, SCC rates were estimated to be 0.96% from an observational study by Oh *et al.*, (2010)[44] and 1.02% when relapse is incorporated.

The MS reports that hot flushes were the most common adverse event on both treatment arms. The rate of hot flushes varied considerably in the trial data from 10% to 63%. During the clarification process the manufacturer provided an MTC for hot flushes which is reported in section 4.2.6 of this report. The MS did not include any data in relation to the costs of treating hot flushes or the HRQoL associated with hot flushes. The MTC presented in the MS clarification showed that there was no statistically significant difference in the rate of hot flushes between the degarelix and comparator arms. Hence the exclusion of the adverse event hot flushes from the economic model is considered acceptable.

ERG critique

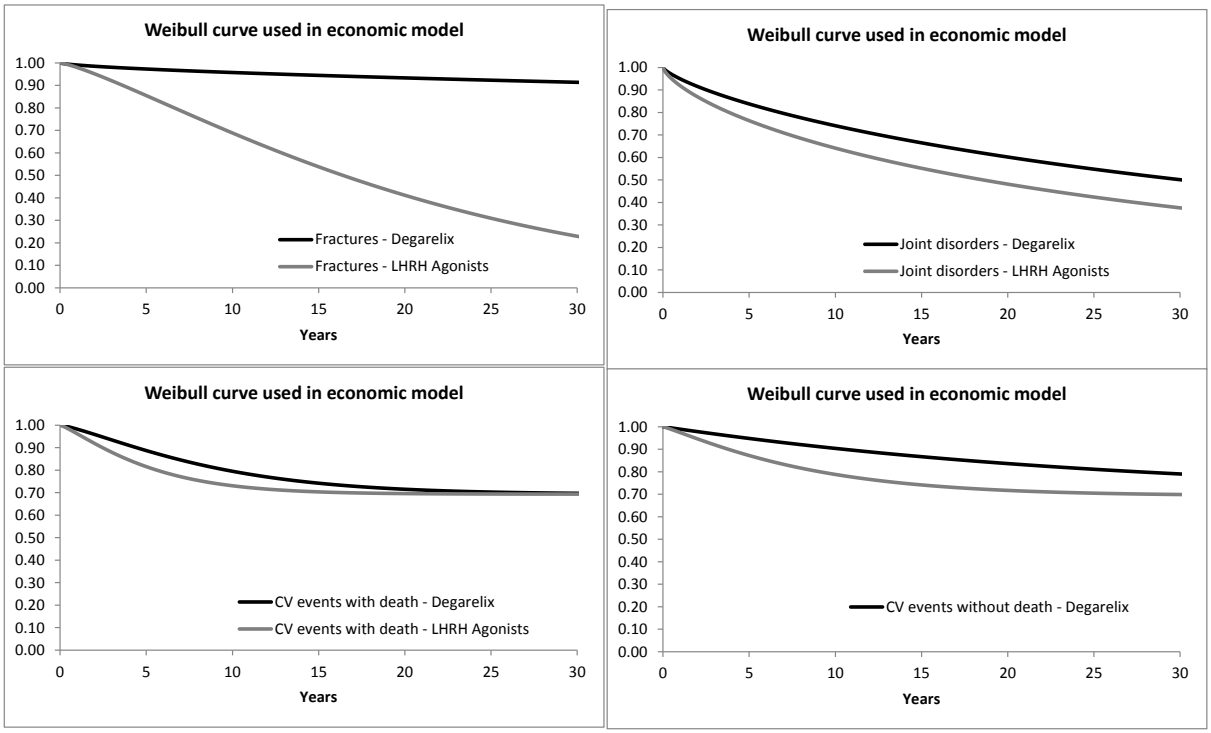
The MS does not provide justification for assuming that the adverse event profiles are the same for each of the LHRH agonists. The ERG believes that data on the adverse events rates of each LHRH agonist should be considered individually. It would also be more appropriate to undertake a meta-analysis rather than simple pooling. As discussed previously, the simple pooling approach breaks randomisation and does not correctly represent the heterogeneity between the six trials. The MS considered fitting exponential and Weibull curves. The ERG believe that the fit of the Weibull curves is poor and the analysis should compare the fit of other parametric curves.

Clinical advice received by the ERG suggests that the extrapolation of the data on joint related signs and symptoms and cardiovascular events could be reasonable. Clinical advice received by the ERG suggests that the rate of fractures would be likely to increase over time for both the degarelix and LHRH agonist groups. This is because suppressed testosterone levels will lead to a reduction in bone mineral density over time. As the model fitted within the MS extrapolates data from just one year, the ERG believes that this clinical opinion should be incorporated such that long term effects are more plausibly represented. The data presented in Figure 29 of the MS has no events after around 112 days for the degarelix arm. Clinical advice received by the ERG indicates that this is not what would be expected in clinical practice. The MS does not provide the individual patient data nor does it provide an

explanation regarding why the flat line occurs. The extrapolation of the AE data using Weibull curves is presented in Figure 17 below. This demonstrates that the model used results in a very large difference in the modelled number of fractures between the degarelix and LHRH agonist arms.

The majority of the RCTs do not report the rate of the SCC adverse events. In the CS21 trial there was one event in the leuprorelin arm and no events on the degarelix arm. The Oh[44] study reports SCC rates of 3/321=0.9%, 4/491=0.8% and 8/754=1.0% for no anti-androgen use and anti-androgen use 0-6 days prior and 7 or more days prior respectively. The ERG believes that the size of the Oh[44] study means that it is a useful source of data for SCC rates.

Figure 17: Extrapolation of adverse event data to 10 years using Weibull curves reported in the MS



5.2.8 Resources and costs

A systematic search of resource use data sources was undertaken and relevant costs from included studies were presented in the MS. Drug costs were taken from the BNF for: degarelix; LHRH agonists; and bicalutamide for flare protection. It was assumed that the mode of administration of degarelix/LHRH agonists was 50% by a practice nurse in a GP surgery and 50% by a nurse in a hospital. Treatment initiation costs are assumed to consist of a CT and bone scan, a PSA test and an urologist outpatient appointment (initial prescription). Following the initial prescription, follow-up appointments with an urologist were assumed to

occur every six months, at which time a PSA test is administered. Table 34 shows the costs associated with each comparator including the drug cost, administration costs and testing. The less expensive regimens are shown in black with the others presented in grey.

Table 34. Costs associated with each comparator including the drug cost, administration costs and testing (Adapted from MS Table 43)

	Cost including drug, administration & testing	
Comparator	**Cost on initiation**	**Cost per 28 days after initiation**
Degarelix: Firmagon	£529.63	£157.69
Leuprorelin 3-monthly: Prostap	£347.94	£95.46
Leuprorelin monthly: Prostap	£347.94	£103.56
Goserelin 3-monthly: Zoladex	£351.03	£98.55
Goserelin monthly: Zoladex	£337.70	£93.32
Goserelin monthly: Novgos	£331.20	£86.82
Triptorelin 3-monthly: Decapeptyl	£341.70	£89.22
Triptorelin monthly: Decapeptyl	£341.70	£97.32
Triptorelin monthly: Gonapeptyl	£354.39	£110.01
Triptorelin 6-monthly:Decapeptyl	£341.70	£87.20

The costs of AEs were calculated based on NHS Reference Costs (2011/2012) and personal social services research unit (PSSRU) costs. These were validated by UK clinicians. The costs are summarised in the Table 35.

Table 35. Summary of adverse event costs used within model (Adapted from MS Table 51)

Adverse events	Hospital costs
CV event	£1,504.77 for a non-fatal event + £52.73 follow-up per year £1,704.41 for a fatal event
Fracture	£375.05 for a mild fracture £1,419.96 for a moderate fracture £8,493.52 for a severe fracture + £182.85 per year follow-on costs while in pain
	£3,471.08 for a fracture on average
Join-related signs and symptoms	£86 for a mild case £923.27 for a moderate case £1,352.05 for a severe case + £549.72 per year follow-on costs while in pain
	£496.64 on average
SCC	£1,459.95 for radiotherapy £25,293.83 for surgery £34 per day for home care £158 per week in a nursing home

Treatment costs are sourced from eMIT and *BNF* and all other costs are sourced from NHS Reference Costs, the PSSRU or the published literature. The resource use and costing assumptions presented in the table were validated by UK clinicians. The costs associated with each of the model health states are detailed in Table 36 below.

Table 36. Costs associated with each of the model health states (adapted from MS Table 44)

Health states	Items	Value
First-line treatment	Technology	Degarelix: £260 first 28 days, £129.37 per 28 days thereafter Goserelin 3 monthly: £81.40 first 28 days, £78.33 per 28 days thereafter
	Staff	£12.14 per 28 days, 56 or 84 days depending on treatment regime On initiation: £93.96 and 6-monthly thereafter
	Tests	On initiation: £67.14 + £105.45 + £3.09 6 monthly: £3.09
	Total	Degarelix: £529.63 on initiation, £157.69 per 28 days thereafter Goserelin 3 monthly: £351.03 on initiation, £98.55 per 28 days thereafter
Anti-androgen addition	Technology	Degarelix: £135.96 per 28 days Goserelin 3 monthly: £84.92 per 28 days
	Staff	£12.14 per 28 days, 56 or 84 days depending on treatment regime On initiation: £93.96 and 3-monthly thereafter

Health states	Items	Value
	Tests	On initiation: £67.14 + £105.45 + £3.09 3 monthly: £3.09
	Total	Degarelix: £399 on initiation, £173.86 per 28 days thereafter Goserelin 3-monthly: £347.96 on initiation , £114.73 per 28 days thereafter
Anti-androgen withdrawal	Technology	Degarelix: £135.96 per 28 days Goserelin 3-monthly: £84.92 per 28 days
	Staff	£12.14 per 28 days, 56 or 84 days depending on treatment regime On initiation: £93.96 and 3-monthly thereafter
	Tests	On initiation: £67.14 + £105.45 + £3.09 3 monthly: £3.09
	Total	Degarelix: £399 on initiation , £173.86 per 28 days thereafter Goserelin 3-monthly: £347.96 on initiation , £114.73 per 28 days thereafter
First-line chemotherapy	Technology	Per 3 weekly session: 75 mg/m2 docetaxel Mean body surface area 1.8m2 1.7 x 80 mg vials at £32.40 per vial Total docetaxel: £54.68 12 x 2 mg tablets of dexamethasone at £0.04 per tablet Total docetaxel: £0.43 42 x 5 mg tablets of prednisolone per day at £0.01 per tablet Total prednisolone: £1.51 Total of 7.3 sessions on average per course[97] Total drug cost per course: £405.13
	Staff	£113.17 oncologist visit per 3 weekly session £826.14 per course
	Tests	On initiation & withdrawal: £89.52 bone scan, £140.59 CT scan, £192.68 MRI On initiation: £3.09 blood test, £637.28 per course
	Adverse events and concomitant medication	Blood, bisphosphonates, epoetin and G-CSF: £683.17 per course
	Total	£3,426.87 per course
Second line chemotherapy	Technology	4 x 250mg tablets abiraterone per day at £24.42 per tablet 2 x 5 mg prednisolone tablets per day at £0.01 per tablet £2,735.19 per 28 days
	Staff	£113.17 oncologist every 3 weeks
	Tests	On initiation & withdrawal and every 6 weeks for 5% of patients: £89.52 bone scan, £140.59 CT scan, £192.68 MRI On initiation and once every 6 weeks: £3.09 blood test
	Adverse events and concomitant medication	Bisphosphonates and G-CSF: £56.98 per 28 days Due to high level of censorship in the abiraterone submission adverse event costs could not be included
	Total	£788.17 on initiation + £2,955.69 per 28 days
Supportive Care	Total	£1,754 for follow-on treatment after failing abiraterone + £132.38 per 28 days for supportive care

Health states	Items	Value
Palliative Care	Total	£4,182.51 for 3 months prior to death – applied on death

ERG critique

The MS uses a cost for 28 days bicalutamide of £3.07 taken from eMIT (12 month period ending November 2012) however the current eMIT price is £1.87 (12 month period to end June 2013) and the current BNF price is £2.54. The ERG notes that the model results are not sensitive to this cost.

The model assumes that 50% of patients with SCC will receive surgery however; clinical advice received by the ERG suggests the surgery rate may be less than 20%.

The MS presents the total average costs for CV event, fracture and joint-related signs and symptoms but the total average cost for SCC is not reported. The ERG calculated the average cost associated with SCC from the model. Greater costs occur in cycle 1, in line with when surgery and radiotherapy take place. A proportion of patients (those with paraplegia or continues symptoms) will continue to incur costs for the remainder of their lifetime. The economic model applies a weekly care cost for ambulant patients (mild SCC) and non-ambulant patients (severe SCC) of £104 and £1097 respectively. However these costs are incorrectly listed in the report as daily costs in Table 32. The source of these values is not described in the MS. In addition these costs which may originate from Table 42 differ from the values reported in Tables 48 and 51. The total discounted cost associated with SCC is £1,836 in the original MS and the proportion of persons experiencing SCC adverse event was 1.02% hence the average discounted cost associated with treating one patient with SCC is £182,647.

The ERG notes that in the MS the cost of surgery per patient is listed as £25,293.83 (MS page 182; Table 48); this is incorrect. However, in the model a cost of £12,153.69 is applied; this is derived from the £9,350 cost estimate referenced. The difference could reflect time spent in hospital following surgery but this is not transparent.

5.2.9 Cost effectiveness results

The MS clarification response presents the cost-effectiveness results for degarelix compared with each of the LHRH agonists. These results use a version of the model in which the manufacturer has corrected an error identified by the ERG in which the transition probability

formulae which differed between degarelix and the LHRH agonists. In these analyses each of the LHRH agonists is assumed to have the same efficacy and adverse events profile.

Table 37: Deterministic base case results [adapted from MS clarification Table D6]

Treatment arm	Totals			Inc. costs	Inc. QALYs gained	Inc. life-years gained	Cost per QALY gained
	Costs	QALYs gained	Life-years gained				
Leuprorelin 3-monthly (Prostap)	£27,479	5.28	9.21				Dominating
Degarelix	£25,939	5.86	9.58	-£1,540	0.58	0.37	
Goserelin 3-monthly (Zoladex)	£27,636	5.28	9.21				Dominating
Degarelix	£25,939	5.86	9.58	-£1,697	0.58	0.37	
Triptorelin 3-monthly (Decapeptyl)	£27,162	5.28	9.21				Dominating
Degarelix	£25,939	5.86	9.58	-£1,223	0.58	0.37	
Leuprorelin monthly (Prostap)	£27,872	5.28	9.21				Dominating
Degarelix	£25,939	5.86	9.58	-£1,933	0.58	0.37	
Goserelin monthly (Novgos)	£27,022	5.28	9.21				Dominating
Degarelix	£25,939	5.86	9.58	-£1,083	0.58	0.37	
Goserelin monthly (Zoladex)	£27,352	5.28	9.21				Dominating
Degarelix	£25,939	5.86	9.58	-£1,413	0.58	0.37	
Triptorelin monthly (Gonapeptyl)	£28,199	5.28	9.21				Dominating
Degarelix	£25,939	5.86	9.58	-£2,260	0.58	0.37	
Triptorelin monthly (Decapeptyl)	£27,555	5.28	9.21				Dominating
Degarelix	£25,939	5.86	9.58	-£1,616	0.58	0.37	
Triptorelin 6-monthly (Decapeptyl)	£27,075	5.28	9.21				Dominating
Degarelix	£25,939	5.86	9.58	-£1,136	0.58	0.37	

The model also includes a subgroup analysis modelling only the effects of degarelix and LHRH agonists in the higher-risk PSA >20 ng/ml population and in the subgroup with baseline cardiovascular disease which are presented in Tables 38 and 40.

Table 38 Results for the PSA >20 ng/ml population [MS Table 60]

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	£28,306	5.36	9.22	-£1,489	0.58	0.44	Dominating

Key: ICER =incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life-years

Table 39 Results for the PSA>20ng/ml population with MS corrected model

Treatment arm	Totals			Incrementals			Cost per QALY	Cost per Life Year	Incremental Net Benefit
	Costs	QALYs gained	Life Years	Costs	QALYs gained	Life Years			
Goserelin 3 Monthly (Zoladex)	£29,794	4.775	8.78	-£1,691	0.59	0.44	**Dominating**	Dominating	£13,395
Degarelix	£28,104	5.360	9.22						

Table 40 Results for the subgroup with baseline cardiovascular disease [MS Clarification D3]

Treatment arm	Totals			Inc. costs	Inc. QALYs gained	Inc. life-years gained	Cost per QALY
	Costs	**QALYs gained**	**Life-years gained**				
Goserelin 3-monthly (Zoladex)	£24,492	4.23	7.22				£4,216
Degarelix	£31,348	5.86	9.58	£6,856	1.63	2.36	

5.2.10 Sensitivity analyses

The MS considered uncertainty around the following structural assumptions:

'Comparator: *sensitivity analysis comparing degarelix to the cheapest and most expensive LHRH agonists currently used in the UK were presented. The sensitivity analysis conducted assumes equal efficacy between LHRH agonists as per the mixed treatment comparison presented in Section 6.7 and evidence from the literature to support the assumption of a class effect. Therefore, the only variation between comparator treatments is in the cost of drugs and resource use.*

Modeling of treatment efficacy: *within the model base case, the long-term efficacy of degarelix in terms of PSA progression is based on extrapolation from the clinical trial data. Within sensitivity analysis, the curve chosen for the extrapolation is tested along with the assumption that benefit continues long term. One scenario analysis investigates the impact of setting the efficacy of degarelix equal to LHRH after one year (that is, no sustained benefit following the end of CS21). Sensitivity analysis is also conducted to examine the impact of assuming no difference in PSA progression between the two treatments, in which case benefits are derived solely from preventing MSEs and cardiovascular events. This analysis presents a worst-case scenario.*

Modeling of mortality: *within the base-case analysis, it is assumed that metastatic patients who progress experience a higher rate of mortality than those who do not, based on available literature. The impact of assuming the same rate of mortality for progressed and non-progressed patients is tested. Additionally, the model includes the option to base mortality on general population life tables rather than prostate-cancer-specific estimates.*

Treatment continuation: *within the base-case analysis, it is assumed that treatment continues until patients progress beyond advanced disease, in line with the license for degarelix. In some UK centers, LHRH or degarelix treatment is actually continued until death. The impact of continuing treatment until death is modeled.*

Setting of care: *the impact of assuming treatment is carried out by practice nurses or wholly in a hospital setting is tested.*

Modeling of MSEs: *there is an option to include MSEs within the model structure or to remove them. Additionally, the curve choice for the time to MSEs is included in a sensitivity analysis as is the type of MSEs included (solely those that were significantly different between the treatments or all events). Within the base case model, the proportion of patients experiencing mild, moderate and severe events is set equal in both arms, sensitivity analysis is conducted using separate trial results for each arm.*

Modeling of cardiovascular events: *within the base case, it is assumed that patients with a history of CVD have a higher risk of fatal and non-fatal cardiovascular events when receiving LHRH agonists than when not receiving LHRH agonists. The impact of assuming the same rate of cardiovascular events for both arms is tested in a sensitivity analysis, as is the curve choice used to model the time to events.*

Utilities: *the model includes the option to use utilities derived primarily from the literature or from alternative utility mappings, using the SF-12 and EORTC QLQ C30 from the CS21 trial.*

Anti-androgen choice: *the model includes the option to analyse the effects of using cypterone acetate rather than bicalutamide for both flare cover and anti-androgen addition.*

Abiraterone: *the impact of inclusion of abiraterone as second-line treatment following docetaxel chemotherapy is tested in sensitivity analysis.'* (MS page 186)

The MS presents the following result of the sensitivity analyses. These results were produced using the uncorrected model and were not updated when the model was corrected.

Table 41: Deterministic model results for sensitivity analyses on parameter values (replicated from MS Table 59)

Parameter	Base case	Sensitivity analysis	ICER	Incremental net benefit (threshold £20,000)
Base case	N/A	N/A	Dominating	£13,068
Varying the comparator				
First-line LHRH agonist	Goserelin 10.8mg (Zoladex)	Goserelin 3.6 mg (Novgos) *lowest-cost comparator*	Dominating	£12,454
		Triptorelin 3.75 mg (Gonapeptyl) *highest-cost comparator*	Dominating	£13,632
Varying treatment efficacy assumptions				
Variation of the parametric curve chosen				
Curve choice for first-line time to PSA progression	Log-normal	Log-logistic	Dominating	£12,907
		Gompertz	Dominating	£13,024
		Exponential	Dominating	£12,554
		Weibull	Dominating	£12,093
Variation in the duration of differential efficacy				
Duration for which hazard ratio applied	For the duration patients remain on first-line therapy	Efficacy of degarelix and LHRH agonists assumed to be equal	£12,987	£804
		For one year; the duration for which there is comparative trial data	£3,751	£3,933
Varying the approach to modelling mortality				
Mortality	i) Increased hazard of mortality post-progression for metastatic patients	No increased hazard of mortality post-progression for metastatic patients	Dominating	£11,542
	ii) Prostate cancer specific mortality incorporated	i) No increased hazard of mortality post-progression for metastatic patients ii) General population mortality incorporated	Dominating	£16,870
Varying the approach to modelling Musculoskeletal Adverse Events				
Inclusion/ exclusion of MSE's from the model structure				
MSE's incorporated	Fractures, joint-related signs and symptoms and spinal cord compression incorporated in the model	Include no MSEs	£2,484	£8,625
		Include all MSEs[a]	Dominating	£12,887
Variation in the parametric curve used to model MSEs over time				
Parametric curve for MSEs	Weibull	Exponential	Dominating	£13,143
Variation of proportion of mild, moderate and severe MSEs across both arms				
Proportion of	Equal across	Proportions as seen	Dominating	£13,158

Parameter	Base case	Sensitivity analysis	ICER	Incremental net benefit (threshold £20,000)
Mild, Moderate and Severe MSEs	both arms	in trial		
Varying the approach to modelling cardiovascular (CV) adverse events				
Inclusion/exclusion of CV events from the model structure	CV events incorporated	CV events not incorporated	Dominating	£12,804
Curve choice for CV event	Exponential	Weibull	Dominating	£13,159
Varying the source used for utilities				
Utility values i) First-line utilities ii) Post-progression utilities iii) Chemotherapy, abiraterone and palliative care utilities iv) Adverse event utilities	i) Kontodimopoulos Algorithm[b] ii) Kontodimopoulos Algorithm[b] iii) Sourced from systematic search iv) Kontodimopoulos Algorithm[b]	i) McKenzie Algorithm[c] ii) McKenzie Algorithm[c] iii) Sourced from systematic search iv) McKenzie Algorithm[c]	Dominating	£11,242
		i) Gray Algorithm[d] ii) Gray Algorithm[4] iii) Sourced from systematic search iv) Gray Algorithm[d]	Dominating	£9,083
		i) Rowen Algorithm[e] ii) Rowen Algorithm[e] iii) Sourced from systematic search iv) Rowen Algorithm[e]	Dominating	£12,230
		i) Bayoumi *et al.* ii) Bayoumi *et al.* iii) Bayoumi *et al.* iv) Predominantly sourced from literature used by Lu *et al*. (MSEs) and NICE clinical guideline (CV events)	Dominating	£14,971
Variation in treatment and administration practice				
Treatment used for flare cover and anti-androgen addition	Bicalutamide	Cyproterone acetate	Dominating	£13,102
Treatment with LHRH and degarelix takes place in	50% primary care; 50% secondary care	All treated in primary care	Dominating	£12,996
		All treated in secondary care	Dominating	£13,141

Parameter	Base case	Sensitivity analysis	ICER	Incremental net benefit (threshold £20,000)
Incorporation of abiraterone	Incorporated in the treatment pathway	Not incorporated	£2,072	£10,658
Stopping rule	Stop treatment on degarelix/ LHRH agonist when castrate/ resistant, in line with the licensed indication	Don't stop treatment until death	Dominating	£12,030
Varying the time horizon				
Time horizon	30 Years	5 years	Dominating	£4,882
		10 Years	Dominating	£9,800
		20 Years	Dominating	£12,968

[a] Including those not incorporated in the base-case as not statistically significant different between treatment arms in the pooled trials or because of evidence of dose-dependency.
[b] EORTC-C30 to EQ-5D using data from gastric cancer patients
[c] EORTC-C30 to EQ-5D using data from inoperable oesophageal cancer patients
[d] SF-36 to EQ-5D using data from the general UK population
[e] EORTC-C30 to EORTC-8D using data from patients with newly diagnosed with multiple myeloma

Following an ERG request for clarification, the manufacturer provided an additional analysis which explores the assumption that all patients receive each treatment line if they are still alive. The scenario analysis assumes that (1) 70% of patients receive docetaxel after failure of treatment on anti-androgen withdrawal, the remaining 30% moving to supportive and palliative care; and (2) 70% of patients receive abiraterone following failure of treatment with docetaxel, the remaining 30% moving to supportive and palliative care. This analysis (which was run with the corrected model) reduced the total costs considerably in both options (by approximately £4,000) and reduces expected QALYs in both arms by approximately 0.05. The incremental costs change significantly from -£1697 to -£322 but the change to incremental QALYs is negligible.

Table 42: Scenario analysis with 70% of patients going on to receive each of docetaxel and abiraterone (from MS clarification response D4)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
Goserelin 3 Monthly (Zoladex)	£22,275	5.23	9.17				
Degarelix	£21,953	5.82	9.55	-£322	0.59	0.38	Dominating

The MS includes a probabilistic sensitivity analysis which samples from uncertain distributions for the majority of the model parameters. The MS clarification response included

updated PSA result which applied lognormal distributions for some hazard ratio and unit cost parameters for which uncertainty had previously been represented using uniform distributions. The PSA results showed that assuming willingness-to-pay thresholds of £30,000 and £20,000 per QALY gained, the probability of degarelix being cost effective was 100% and 99.9% respectively. The probability that degarelix was cost-saving was 91.5%.

ERG critique

The set of sensitivity analyses presented in the MS address many of the key areas of structural uncertainty within the model. The model used to undertake the PSA was not provided by the manufacturer and so this could not be checked by the ERG.

5.2.11 Model validation

The MS reports that the economic model was validated by leading healthcare professionals and reviewed internally by an economist who had not been involved in the development of the model. One year outcomes were compared to clinical trial data for: overall survival; PSA progression; fractures; joint-related signs and symptoms; and cardiovascular events.

ERG critique

The ERG validated the model by reproducing selected sensitivity and scenarios analyses and checking that the results changed in the expected manner. This process identified an erroneous difference in the formulae for the transition probabilities formula used for degarelix and the LHRH agonists. This error was corrected by the manufacturer and a corrected model was provided. No other inconsistencies were found with the results presented by the manufacturer. The ERG noted inconsistencies in the reporting of model parameter values. In particular the SCC treatment costs were confusingly reported with different values reported in different places within the MS and no average cost presented.

The ERG suggests that model validation undertaken by the manufacturer was not comprehensive. Considering the plausibility of the extrapolation of data beyond the trial period is a key part of the validation process. The healthcare professionals consulted by the manufacturer did not review the plausibility of the extrapolation of AE data beyond the clinical trial period. The ERG considers that a robust validation using the comparison of model predictions and trial outcomes at one year (MS Table 52) was not possible as uncertainty surrounding the observed data was not presented.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Details of additional work conducted by the ERG in relation to cost effectiveness are provided together with a summary table reporting the impact on ICER values. Detailed explanations of exploratory analyses are provided in Appendix 6 to allow replication of analyses. The ERG notes that these analyses only address some of the issues identified within the MS. It was not possible to address all issues due to limitations of the manufacturer's model structure and assumptions.

ERG suggested base case analysis

Given the issues highlighted and discussed earlier in this chapter, analyses were conducted taking account of the following alterations to the model simultaneously:

- 3-monthly triptorelin which is the least expensive LHRH agonist of all the 1- and 3-monthly formulations
- LHRH agonists and degarelix are assumed to be administered until death; this is consistent with usual clinical practice and the licensed indication.
- The hazard ratio for differential efficacy was applied with a one-year duration (in line with evidence from trial).
- 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%. This is consistent with data provided in the MS clarification response (page 21).

Additional scenario analyses run by the ERG included:

The following additional scenarios analyses were undertaken using the ERG-preferred version of the model.

- Analyses were undertaken assuming patient age of 65 and 80 years.
- Variations in treatment pathway: an analysis was undertaken in which the proportion of patients receiving chemotherapy after PSA progression was reduced to 40% and the proportion of patients receiving abiraterone was reduced to 40%
- An exploratory analysis was undertaken in which SCC adverse events are excluded from the analysis.
- An analysis was undertaken assuming 6-monthly triptorelin (the least expensive of all the LHRH agonists)
- An exploratory analysis was undertaken which assumes that the rate of fractures is the same for both the degarelix and LHRH agonist arms (the Weibull curve in the MS for LHRH agonists was used for both arms).

- An analysis was undertaken in which metastatic patients who progress from first-line treatment are assumed to have no increased risk of mortality. The evidence linking PSA progression and overall survival is inconclusive.
- A subgroup analysis was undertaken for 'patients with spinal metastases with impending or actual SCC.'
- An analysis was undertaken whereby PSA progression rates were assumed to be the same for degarelix and LHRH agonists.

Note that all of these scenario analyses use the ERG suggested base case described above as the starting point.

Clinician advice received by the ERG suggests that the use of degarelix in the subgroups 'patients with spinal metastases with impending or actual SCC' and 'patients with high tumour volume with impending or actual urinary outflow obstruction' could potentially be appropriate. An exploratory analysis was also undertaken for the 'patients with spinal metastases with impending or actual SCC' which considered the circumstances under which degarelix may be cost-saving. An analysis was also undertaken in which the base case analysis was modified to exclude SCC adverse events; this analysis could be representative for a subgroup with no risk of SCC.

5.4 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The ERG suggested base case analysis is presented in Table 43 with full results provided in Appendix 5.

Table 43: Results of ERG base case analysis

ERG base case: 3-monthly triptorelin , LHRH agonists and degarelix administered until death , One year duration for which the hazard ratio for differential efficacy applied , The proportion of patients receiving chemotherapy after PSA progression was 70% and the proportion of patients receiving abiraterone was 70%									
Treatment Arm	Totals			Incrementals			Cost per QALY	Cost per Life Year	Incremental Net Benefit (Threshold £20,000 per QALY)
	Costs	QALYs Gained	Life Years Gained	Costs	QALYs Gained	Life Years Gained			
Triptorelin 3 Monthly (Decapeptyl)	£22,649	5.570	9.39	£3,659	0.247	0.16	**£14,798**	£22,323	£1,286
Degarelix	£26,308	5.818	9.55						

The ERG base case was associated with an additional cost of £3,659 and a QALY gain of 0.25 and an ICER of £14,798 per QALY gained.

Additional scenario analyses run by the ERG are presented in Table 43. Note that these scenario analyses all work from the ERG suggested base case described above. . The analyses demonstrated that this ICER was very sensitive to four model assumptions: (1) the exclusion of SCC adverse events from the analysis, (2) the modelling of fracture rates, (3) the assumption that PSA progression affects mortality rates in metastatic patients, and (4) the assumption of equal efficacy of degarelix and LHRH agonists. The ICER values obtained with these three assumptions were £25,486, £21,950, £17,067, and £35,589 per QALY gained respectively.

Table 44 Additional scenario analyses run by the ERG

Treatment Arm	Totals			Incrementals			Cost per QALY	Cost per Life Year	Incremental Net Benefit (Threshold £20,000 per QALY)
	Costs	QALYs Gained	Life Years Gained	Costs	QALYs Gained	Life Years Gained			
· **Patient age of 65 years**									
Triptorelin 3 Monthly (Decapeptyl)	£27,547	6.632	12.12	£4,436	0.296	0.22	**£14,961**	£20,040	£1,494
Degarelix	£31,983	6.929	12.35						
· **Patient age 80 years**									
Triptorelin 3 Monthly (Decapeptyl)	£16,276	4.160	6.36	£2,595	0.178	0.10	**£14,607**	£25,989	£958
Degarelix	£18,872	4.338	6.46						
· **An exploratory analysis in which SCC adverse events are excluded from the analysis.**									
Triptorelin 3 Monthly (Decapeptyl)	£20,785	5.601	9.39	£5,523	0.217	0.16	**£25,486**	£33,690	-£1,189
Degarelix	£26,308	5.818	9.55						
· **6 monthly Triptorelin (the cheapest of all the LHRH agonists)**									
Triptorelin 6 Monthly (Decapeptyl)	£22,539	5.570	9.39	£3,769	0.247	0.16	**£15,243**	£22,994	£1,176
Degarelix	£26,308	5.818	9.55						
· **An exploratory analysis which assumes that the rate of fractures is the same for both the degarelix and LHRH agonist arms. (The Weibull curve in the MS for LHRH agonists was used for both arms.)**									
Triptorelin 3 Monthly (Decapeptyl)	£22,649	5.570	9.39	£4,565	0.208	0.16	**£21,950**	£27,850	-£406
Degarelix	£27,214	5.778	9.55						
· **Variations in treatment pathway: an analysis in which the proportion of patients receiving chemotherapy after PSA progression was reduced to 40% and the proportion of patients receiving abiraterone was reduced to 40%**									
Triptorelin 3 Monthly (Decapeptyl)	£19,823	5.539	9.36	£3,895	0.249	0.17	**£15,674**	£23,586	£1,075
Degarelix	£23,718	5.787	9.53						
· **Metastatic patients who progress from first-line treatment have no increased risk of mortality. The evidence linking PSA progression and overall survival is inconclusive.**									
Triptorelin 3 Monthly (Decapeptyl)	£24,021	5.745	9.97	£3,567	0.209	0.07	**£17,067**	£52,992	£613
Degarelix	£27,588	5.954	10.03						
· **Efficacy of degarelix and LHRH agonists assumed to be equal.**									
Triptorelin 3 Monthly (Decapeptyl)	£22,142	5.701	9.49	£4,166	0.117	0.05	**£35,589**	£76,000	-£1,825
Degarelix	£26,308	5.818	9.55						

The ERG undertook exploratory analyses which considered the subgroup: 'patients with spinal metastases with impending or actual SCC'. There are no data comparing the efficacy of degarelix with LHRH agonists for this subgroup. However, the ERG undertook an exploratory analysis which relied on two assumptions. Firstly, the analysis is based on the assumption reported in the MS that SCC adverse events will not occur with treatment with degarelix. Secondly, the efficacy (in terms of PSA progression and OS) is (conservatively) assumed to be the same for degarelix and LHRH agonists. The rate of SCC in the subgroup is not known so results for several values are presented. Details of the analysis are presented in Table 45. Under the assumption of equal PSA progression and OS efficacy, the QALY gains associated with degarelix will be higher than with triptorelin (due to less QALY decrements associated with SCC events). If the rate of SCC in the subgroup is over 3.5% then degarelix results in a saving in costs and hence it will dominate.

Table 45: Exploratory analysis for the subgroup 'patients with spinal metastases with impending or actual SCC

Subgroup with spinal metastases with impending or actual spinal cord compression			
SCC rate in the subgroup	5%	10%	50%
Average cost of treating one person with SCC	£182, 647	£182,647	£182,627
Average cost of treating SCC	£9,132	£18,265	£91,324
Incremental costs associated with treatment and administration with degarelix compared to triptorelin 3-monthly	£6,396	£6,396	£6,396
Cost saving associated with addition of degarelix (incorporating degarelix/LHRH agonist treatment costs and SCC treatment costs)	£2,737	£11,869	£84,928

5.5 Conclusions of the cost effectiveness section

The submission was considered to be complete with respect to the identification and consideration of relevant published cost-effectiveness studies. The ERG believe that the *de novo* economic evaluation had several significant limitations and that the MS does not contain an unbiased estimate of the technology's ICER in relation to relevant populations, interventions comparators and outcomes.

The major issues with the MS *de novo* economic model are:

- The model has a Markov-treatment sequence structure which assumes an identical treatment sequence is followed by all patients. As there is variation in the treatment sequence between patients, this model structure is inappropriate. The ERG considers

that a model structure that explicitly models time to metastatic disease and time to death would have been more transparent, appropriate and flexible.

- LHRH agonists were considered equivalent in terms of efficacy and adverse events without adequate justification. The ERG believes that the efficacy and adverse events of each LHRH agonist should be modelled individually.
- Bicalutamide monotherapy was not included as a comparator within the MS.
- The analysis of the adverse event data was inappropriate. Firstly, the analysis should have been based on a meta-analysis rather than simple pooling. Secondly, the analysis should compare the fit of additional parametric curves as the fit of the Weibull which was used in the manufacturer's model was poor for some adverse events. The ERG was unable to address these issues as the individual patient data were not supplied.

The direction and magnitude of the bias associated with these issues is not clear.

The major issues with the data used to inform the MS *de novo* economic analysis are:

- The OS benefit associated with degarelix is associated with considerable uncertainty. The duration of the clinical trials was inappropriate to determine overall survival benefit. The data supporting the relationship between PSA progression and overall survival is inconclusive.
- The data on PSA progression and adverse events is for a maximum of one-year duration so the model is based on extrapolation of these data which introduces considerable uncertainty.
- The frequency of flare protection was considerably lower in the trials than is normal in clinical practice in the UK.

The MS base case analysis for degarelix compared to triptorelin (3-monthly) resulted in a cost saving of £1,223 and a QALY gain of 0.58; in this analysis degarelix was dominating. A subgroup analysis for patients with PSA>20ng/ml resulted in a cost saving of £1,489 and a QALY gain of 0.44; again, degarelix was expected to be dominating. A subgroup analysis for patients with baseline cardiovascular disease resulted in incremental costs of £6,856, incremental QALYs of 1.63 and an ICER of £4,216 per QALY gained. The ERG were concerned that the base case analysis provided in the original MS did not represent an unbiased estimate of the technology's ICER.

The additional analyses undertaken by the ERG demonstrates the impact of several key assumptions on the ICER. The ERG base case analysis considered: 3-monthly triptorelin as a

comparator; assumed LHRH agonists treatment was continued until death; assumed the hazard ratio for differential efficacy applied for one year; assumed the proportion of patients receiving chemotherapy after PSA progression was 70%; and the proportion of patients receiving abiraterone was 70%. The ERG base case was associated with an additional cost of £3,659 and a QALY gain of 0.25 and an ICER of £14,798 per QALY gained.

ERG scenario analyses demonstrated that this ICER was very sensitive to four model assumptions: (1) the exclusion of SCC adverse events from the analysis; (2) the modelling of fracture rates; (3) the assumption that PSA progression affects mortality rates in metastatic patients; and (4) the assumption of equal efficacy of degarelix and LHRH agonists. The ICER values obtained with these three assumptions were £25,486, £21,950, £17,067, and £35,589 per QALY gained respectively. Finally, an ERG scenario analysis which explored the possible benefits of degarelix for the subgroup 'patients with spinal metastases with actual or impending SCC' suggested that degarelix has the potential to be cost saving for this subgroup.

6 END OF LIFE

Degarelix does not meet the end of life criteria published by NICE. The criteria includes:

- *"the medicine is indicated, in its license for a patient population normally not exceeding 7000 new patients per annum*

As indicated in section 2.1 of this report the patient population exceeds this number.

- *indicated for the treatment of patients with a diagnosis of a terminal illness and who are not, on average, expected to live for more than 24 months*

Section 2.3 of the MS (page 18) describes that 80.2% of this population have five year survival rates.

- *there is sufficient evidence to indicate that the medicine offers a substantial extension to life, compared to current NHS treatment*

There is insufficient evidence from the submitted evidence in section 4 of this report that degarelix offers a substantial extension to life

http://www.nice.org.uk/aboutnice/howwework/devnicetech/endoflifetreatments.jsp

7 CONCLUSIONS

The section should focus on any difference(s) of opinion between the manufacturer and the ERG that might influence the size of the ICER. Priority should be focussed on discussing information that will be useful to the Appraisal Committee including strengths, weaknesses and remaining uncertainties. Further summary of evidence is not required in this section.

7.1 Implications for research

On the basis of the clinical evidence provided in the MS, degarelix has a similar efficacy and safety profile to the LHRH agonists in terms of overall survival. Additionally, the main pivotal trial CS21 showed that degarelix is non-inferior to leuprorelin for reduction of testosterone ≤0.5 ng/ml and that degarelix achieved a more rapid PSA response than leuprorelin.

Whilst the included trials were considered of good quality there were several issues which limits their applicability to the decision problem. Firstly the study population is generally of a lower disease severity than the target population that degarelix is licensed for. Trials included patients with localised and not classifiable as well as locally advanced and metastatic prostate cancer. Secondly that flare protection in the comparator arms was not used consistently as would be used in UK clinical practice. Thirdly that none of the trials were of sufficient design or duration to measure survival and yet conclusions are drawn based on small death rates observed in the trials.

In the MS (page 6) the results of several analyses are reported which are flawed. These claims are:

- That "*degarelix suppresses serum testosterone to castrate levels more rapidly than LHRH agonists (p<0.0001)"* (MS page 6). This analysis is versus leuprorelin only. The manufacturer assumes clinical equivalence of the LHRH agonists: leuprorelin; goserelin and triptorelin on the basis of a meta-analysis of overall survival which did not include triptorelin.

- That "*rates of overall survival at one year are statistically higher with degarelix than with LHRH agonists (p<0.05)*". This analysis does not include triptorelin and includes trial CS35 which is deemed to be not fully applicable to the decision problem.

- That "*degarelix is associated with a statistically lower risk of fractures (p=0.0234) joint-related signs and symptoms (p=0.0116), and urinary tract-related adverse events (p<0.0001)*". This analysis is based on simple pooling from trials which ignored the different baseline characteristics and heterogeneity across the included trials.
- That "*degarelix is associated with a statistically significant 50% lower risk of cardiovascular events – including arterial embolic and thrombotic events, haemorrhagic and ischaemic cerebrovascular conditions, myocardial infarction and other forms of ischaemic heart disease – and cardiovascular-related death (p=0.0023)."* This analysis is based on simple pooling from trials which ignored the different baseline characteristics and heterogeneity across the included trials.

The ERG re-ran the MTC of overall survival which suggested triptorelin was associated with lower mortality than leuprorelin. The ERG considers that the assumption that none of the LHRH agonists demonstrates superior clinical efficacy does not necessarily demonstrate clinical equivalence is both an incorrect assumption and currently remains unproven.

Clinical advisors to the ERG stressed the need for prospective RCTs examining degarelix versus LHRH agonists:

i. in long-term treatment;

ii. in severe disease and in the elderly and frail;

iii. to examine potential benefits for those with high cardiovascular risk.

The ERG identifies the following major issues with the MS *de novo* economic model however, the direction and magnitude of the bias caused by these issues is not clear.

- The model has a Markov treatment sequence structure which assumes an identical treatment sequence for all patients. As there is variation in the treatment sequence between patients this model structure is inappropriate. The ERG considers that a model structure that explicitly models time to metastatic disease and time to death would be more transparent, appropriate and flexible.
- LHRH agonists were considered equivalent in terms of efficacy and adverse events without adequate justification. The ERG believes that the efficacy and adverse events of each LHRH agonist should be modelled individually.
- Bicalutamide monotherapy was not included as a comparator within the MS.

- The analysis of the adverse event data was inappropriate. Firstly, the analysis should undertake a meta-analysis rather than simply pooling. Secondly, the analysis should compare the fit of additional parametric curves and the fit of the Weibull which was used in the MS was poor for some adverse events. The ERG was unable to address these issues as the individual patient data was not supplied.

The ERG suggests that the major issues with the data used to inform the MS *de novo* economic model are:

- The OS benefit associated with degarelix is associated with considerable uncertainty. The duration of the clinical trials was inappropriate to determine overall survival benefit. The data supporting the relationship between PSA progression and overall survival is inconclusive.
- The data on PSA progression and adverse events is for a maximum of one year duration so the modelling is based on extrapolation of these data which introduces considerable uncertainty.
- The frequency of flare protection was considerably lower in the trials than is normal in clinical practice in the UK.

The additional analyses undertaken by the ERG demonstrated that the results presented in the MS may not provide in the original submission did not represent an unbiased estimate of the technology's ICER.

The MS base case analysis for degarelix compared to triptorelin (3-monthly) resulted in a cost saving of £1,223 and a QALY gain of 0.58, hence degarelix dominated. A subgroup analysis for patients with PSA>20ng/ml resulted in a cost saving of £1,489 and a QALY gain of 0.44 A subgroup analysis for patients with baseline cardiovascular disease resulted in incremental costs of £6,856, incremental QALYs of 1.63 and an ICER of £4,216 per QALY gained.

The ERG base case analysis considered: 3-monthly triptorelin as a comparator, assumed LHRH agonists treatment was continued until death, assumed the hazard ratio for differential efficacy applied for one year, and assumed the proportion of patients receiving chemotherapy after PSA progression was 70% and the proportion of patients receiving abiraterone was 70%. The ERG base case was associated with an additional cost of £3,659 and a QALY gain of 0.25 and an ICER of £14,798 per QALY gained.

ERG scenario analyses demonstrated that this ICER was very sensitive to four model assumptions: (1) the exclusion of SCC adverse events from the analysis, (2) the modelling of fracture rates, (3) the assumption that PSA progression affects mortality rates in metastatic patients, and (4) the assumption of equal efficacy of degarelix and LHRH agonists. The ICER values obtained with these three assumptions were £25,486, £21,950, £17,067, and £35,589 per QALY gained respectively. Finally, an ERG scenario analysis which explored the possible benefits of degarelix for the subgroup 'patients with spinal metastases with actual or impending SCC' suggested that degarelix has the potential to be cost-saving for this subgroup.

8. APPENDICES

Appendix 1: Quality Assessment using ScHARR-TAG economic modelling checklist

Title

A statement of the problem

A discussion of the need for modelling

A description of the relevant factors and outcomes

A description of model including: type of model; time frame; perspective; and setting

A description of data sources, with description of respective strengths and weaknesses

Key assumptions relating to model structure and data stated

Disease specific factors included within modelling (Items to be specified in conjunction with expert clinical input)

Validation

Results

Sensitivity analysis results

Appendix 2 Summary of ERG amended, updated and supplementary searches

ERG repeat (translated) and amended searches
12th September 2013

	Clinical effectiveness searches	
No filter*	**MS translated by ERG**	**ERG amended****
Medline and Medline in Process	6390	9832
Embase	8457	10521
Cochrane Library	851	962
WoS	9444	NA
With RCT filter	**MS translated by ERG**	**ERG amended****
Medline and Medline in Process	1874	2673
Embase	2252	2906
Cochrane Library	NA	NA
WoS	1542	NA
Adverse events	**MS translated by ERG**	**ERG created*****
Medline and Medline in Process	5	4342
Embase	13	6177
Cochrane Library	131	455
WoS	15	1379

*Number of records retrieved in the search without filters. The manufacturer used study design filters for retrieving RCTs, systematic reviews/meta-analysis.
**ERG amended search to include Subject Headings (applicable to Medline, Embase and Cochrane Library) as seen in the cost-effectiveness searches
***ERG created AEs search using search techniques from Golder et al., (2006).

Updated 2013 searches
13th September 2013

Database/register search	**2013 Records**
Medline and Medline in Process	464
Embase	663
Cochrane Library	4
WoS	635
Clinicaltrials.gov	26 unique
PubMed	141
Total	1933
Total unique in database	1055

Appendix 3 ERG amended search strategies

Medline and MEDLINE(R) In-Process:Ovid. 1946 to Present
13th September 2013

1. (degarelix or firmagon or abarelix or plenaxis).tw.
2. exp Gonadotropin-Releasing Hormone/
3. exp Hormone Antagonists/
4. 2 and 3
5. ((luteinising or luteinizing or LHRH or gonadotrop$ or GNRH) and (agonist$ or antagonist$ or blocker$)).tw.
6. (androgen deprivation or ADT or androgen suppression).tw.
7. Goserelin/
8. Leuprolide/
9. Triptorelin Pamoate/
10. Buserelin/
11. (goserelin or zoladex or novgos or eulexin or leuprorelin or leuprolide or prostap or lupron or eligard or carcinil or depo-eligard enanton or enantone or ginecrin or leuplin or lucrin or procren or procrin or trenantone or uno-enantone or viadur or triptorelin or trelstar or decapeptyl or gonapeptyl or salvacyl or buserelin or suprefact or suprecur or etilamide or bigonist or profact or receptal or flakon or cinnafact).tw.
12. (bicalutamide or casodex or cosudex or calutide or kalumid or bicalox).tw.
13. exp Androgen Antagonists/
14. 1 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 1 or 5 or 6 or 11 or 12
16. exp Prostatic Neoplasms/
17. ((prostate or prostatic) and (cancer or carcinoma or adenocarcinoma or tumour or tumor or neoplasm$)).tw.
18. 16 or 17
19. 14 and 18
20. 15 and 19
21. 19 not 20

Embase 1974 to 2013 September 12
13th September 2013

1. (degarelix or firmagon or abarelix or plenaxis).tw.
2. degarelix/
3. abarelix/
4. exp gonadorelin/
5. exp hormone antagonist/
6. 4 and 5
7. ((luteinising or luteinizing or LHRH or gonadotrop$ or GNRH) and (agonist$ or antagonist$ or blocker$)).tw.
8. (androgen deprivation or ADT or androgen suppression).tw.
9. goserelin/
10. leuprorelin/
11. triptorelin/
12. buserelin/
13. buserelin acetate/
14. (goserelin or zoladex or novgos or eulexin or leuprorelin or leuprolide or prostap or lupron or eligard or carcinil or depo-eligard enanton or enantone or ginecrin or leuplin or lucrin or procren or procrin or trenantone or uno-enantone or viadur or triptorelin or trelstar or

decapeptyl or gonapeptyl or salvacyl or buserelin or suprefact or suprecur or etilamide or bigonist or profact or receptal or flakon or cinnafact).tw.
15. bicalutamide/
16. (bicalutamide or casodex or cosudex or calutide or kalumid or bicalox).tw.
17. 1 or 2 or 3 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. 1 or 7 or 8 or 14 or 16
19. exp prostate tumor/
20. ((prostate or prostatic) and (cancer or carcinoma or adenocarcinoma or tumour or tumor or neoplasm$)).tw.
21. 19 and 20
22. 17 and 21
23. 18 and 21
24. 22 not 23

Cochrane Library (Wiley Online)
13th September 2013

#1 degarelix or firmagon or abarelix or plenaxis:ti,ab,kw (Word variations have been searched)
#2 MeSH descriptor: [Gonadotropin-Releasing Hormone] explode all trees
#3 MeSH descriptor: [Hormone Antagonists] explode all trees
#4 (luteinising or luteinizing or LHRH or gonadotrop* or GNRH) and (agonist* or antagonist* or blocker*):ti,ab,kw
#5 (androgen deprivation or ADT or androgen suppression):ti,ab,kw
#6 MeSH descriptor: [Goserelin] this term only
#7 MeSH descriptor: [Leuprolide] this term only
#8 MeSH descriptor: [Triptorelin Pamoate] this term only
#9 MeSH descriptor: [Buserelin] this term only
#10 (goserelin or Zoladex or Novgos or Eulexin or leuprorelin or leuprolide or Prostap or Lupron or Eligard or Carcinil or Depo-Eligard Enanton or Enantone or Ginecrin or Leuplin or Lucrin or Procren or Procrin or Trenantone or Uno-Enantone or Viadur or triptorelin or Trelstar or Decapeptyl or Gonapeptyl or salvacyl or buserelin or Suprefact or suprecur or Etilamide or Bigonist or Profact or Receptal or Flakon or Cinnafact):ti,ab,kw
#11 (bicalutamide or Casodex or Cosudex or Calutide or Kalumid or Bicalox):ti,ab,kw
#12 MeSH descriptor: [Androgen Antagonists] explode all trees
#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
#14 #1 or #4 or #5 or #10 or #11
#15 MeSH descriptor: [Prostatic Neoplasms] this term only
#16 (prostate or prostatic) and (cancer or carcinoma or adenocarcinoma or tumour or tumor or neoplasm*):ti,ab,kw
#17 #15 or #16
#18 #13 and #17
#19 #14 and #17
#20 #18 not #19

Web of Science (Thomson Reuters)
13th September 2013

11 #10 AND #9
10 Topic=(((prostate or prostatic) and (cancer or carcinoma or adenocarcinoma or tumour or tumor or neoplasm*)))
9 #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
8 Topic=(androgen antagonist*)

7 Topic=((bicalutamide or casodex or cosudex or calutide or kalumid or bicalox))
6 Topic=((((((((((((((((((((((((((((((goserelin OR zoladex) OR novos) OR eulexin) OR leuprorelin) OR leuprolide) OR prosta) OR lupron) OR eligard) OR carcini) OR depo-eligard enanton) OR enantone) OR ginecrin) OR leuplin) OR lucrin) OR procren) OR procain) OR trenantone) OR uno-enantone) OR vitadur) OR triptorelin) OR telstar) OR decapeptyl) OR gonapeptyl) OR salvacyl) OR buserelin) OR superfast) OR suprecur) OR ethylamide) OR bigonist) OR proact) OR receptal) OR flavon) OR cinnafact)
5 Topic=((goserelin or zoladex or novgos or eulexin or leuprorelin or leuprolide or prostap or lupron or eligard or carcinil or depo-eligard enanton or enantone or ginecrin or leuplin or lucrin or procren or procrin or trenantone or uno-enantone or viadur or triptorelin or trelstar or decapeptyl or gonapeptyl or salvacyl or buserelin or suprefact or suprecur or etilamide or bigonist or profact or receptal or flakon or cinnafact))
4 Topic=((androgen deprivation or ADT or androgen suppression))
3 Topic=(((luteinising or luteinizing or LHRH or gonadotrop* or GNRH) and (agonist* or antagonist* or blocker*)))
2 Topic=(((degarelix OR firmagon) OR abarelix) OR planaxis)
1 Topic=((degarelix or firmagon or abarelix or plenaxis))

PubMed (NCBI, http://www.ncbi.nlm.nih.gov/pubmed)
8th October 2013

#12	Search (#10 and #11)
#11	Search ("2013/03/25"[Date - Publication] : "2013/10/08"[Date - Publication])
#10	Search (#8 and #9)
#9	Search ((prostate or prostatic)) AND (cancer or carcinoma or adenocarcinoma or tumour or tumor or neoplasm)
#8	Search (#1 or #2 or #3 or #4 or #7)
#7	Search (#5 and #6)
#6	Search (agonist* or antagonist* or blocker*)
#5	Search (luteinising or luteinizing or LHRH or gonadotrop* or GNRH)
#4	Search androgen antagonist*
#3	Search (bicalutamide or casodex or cosudex or calutide or kalumid or bicalox)
#2	Search (goserelin or zoladex or novgos or eulexin or leuprorelin or leuprolide or prostap or lupron or eligard or carcinil or depo-eligard enanton or enantone or ginecrin or leuplin or lucrin or procren or procrin or trenantone or uno-enantone or viadur or triptorelin or trelstar or decapeptyl or gonapeptyl or salvacyl or buserelin or suprefact or suprecur or etilamide or bigonist or profact or receptal or flakon or cinnafact)
#1	Search (degarelix or firmagon or abarelix or plenaxis)

ERG searches in Clinicaltrials.gov Register on 13/09/13

1. **4 studies found for**: degarelix | received from 01/01/2013 to 09/13/2013
2. **4 studies found for**: firmagon | received from 01/01/2013 to 09/13/2013
3. **no studies found for**: abarelix | received from 01/01/2013 to 09/13/2013
4. **no studies found for**: plenaxis | received from 01/01/2013 to 09/13/2013
5. **4 studies found for**: goserelin | received from 01/01/2013 to 09/13/2013
6. **4 studies found for**: zoladex | received from 01/01/2013 to 09/13/2013
7. **no studies found for**: novgos | received from 01/01/2013 to 09/13/2013
8. **1 study found for**: eulexin | received from 01/01/2013 to 09/13/2013

9. **1 study found for**: leuprorelin | received from 01/01/2013 to 09/13/2013
10. **10 studies found for**: leuprolide | received from 01/01/2013 to 09/13/2013
11. **10 studies found for**: prostap | received from 01/01/2013 to 09/13/2013
12. **10 studies found for**: lupron | received from 01/01/2013 to 09/13/2013
13. **10 studies found for**: eligard | received from 01/01/2013 to 09/13/2013
14. **10 studies found for**: carcinil | received from 01/01/2013 to 09/13/2013
15. **1 study found for**: depo-eligard enanton | received from 01/01/2013 to 09/13/2013
16. **10 studies found for**: enantone | received from 01/01/2013 to 09/13/2013
17. **10 studies found for**: ginecrin | received from 01/01/2013 to 09/13/2013
18. **10 studies found for**: leuplin | received from 01/01/2013 to 09/13/2013
19. **10 studies found for**: lucrin | received from 01/01/2013 to 09/13/2013
20. **10 studies found for**: procren | received from 01/01/2013 to 09/13/2013
21. **10 studies found for**: procrin | received from 01/01/2013 to 09/13/2013
22. **10 studies found for**: trenantone | received from 01/01/2013 to 09/13/2013
23. **10 studies found for**: uno-enantone | received from 01/01/2013 to 09/13/2013
24. **10 studies found for**: viadur | received from 01/01/2013 to 09/13/2013
25. **7 studies found for**: triptorelin | received from 01/01/2013 to 09/13/2013
26. **7 studies found for**: trelstar | received from 01/01/2013 to 09/13/2013
27. **3 studies found for**: decapeptyl | received from 01/01/2013 to 09/13/2013
28. **1 study found for**: gonapeptyl | received from 01/01/2013 to 09/13/2013
29. **no studies found for**: salvacyl | received from 01/01/2013 to 09/13/2013
30. **3 studies found for**: buserelin | received from 01/01/2013 to 09/13/2013
31. **3 studies found for**: suprefact | received from 01/01/2013 to 09/13/2013
32. **no studies found for**: suprecur | received from 01/01/2013 to 09/13/2013
33. **3 studies found for**: etilamide | received from 01/01/2013 to 09/13/2013
34. **no studies found for**: bigonist | received from 01/01/2013 to 09/13/2013
35. **3 studies found for**: profact | received from 01/01/2013 to 09/13/2013
36. **3 studies found for**: receptal | received from 01/01/2013 to 09/13/2013
37. **1 study found for**: flakon | received from 01/01/2013 to 09/13/2013
38. **no studies found for**: cinnafact | received from 01/01/2013 to 09/13/2013
39. **1 study found for**: bicalutamide | received from 01/01/2013 to 09/13/2013
40. **1 study found for**: casodex | received from 01/01/2013 to 09/13/2013
41. **1 study found for**: cosudex | received from 01/01/2013 to 09/13/2013
42. **no studies found for**: calutide | received from 01/01/2013 to 09/13/2013
43. **no studies found for**: kalumid | received from 01/01/2013 to 09/13/2013
44. **no studies found for**: bicalox | received from 01/01/2013 to 09/13/2013

Appendix 4 ERG supplementary adverse events search strategies

Medline and MEDLINE(R) In-Process:Ovid. 1946 to Present
13th September 2013

1. (degarelix or firmagon or abarelix or plenaxis).tw.
2. exp Gonadotropin-Releasing Hormone/
3. exp Hormone Antagonists/
4. 2 and 3
5. ((luteinising or luteinizing or LHRH or gonadotrop$ or GNRH) and (agonist$ or antagonist$ or blocker$)).tw.
6. (androgen deprivation or ADT or androgen suppression).tw.
7. Goserelin/
8. Leuprolide/
9. Triptorelin Pamoate/
10. Buserelin/
11. (goserelin or zoladex or novgos or eulexin or leuprorelin or leuprolide or prostap or lupron or eligard or carcinil or depo-eligard enanton or enantone or ginecrin or leuplin or lucrin or procren or procrin or trenantone or uno-enantone or viadur or triptorelin or trelstar or decapeptyl or gonapeptyl or salvacyl or buserelin or suprefact or suprecur or etilamide or bigonist or profact or receptal or flakon or cinnafact).tw.
12. (bicalutamide or casodex or cosudex or calutide or kalumid or bicalox).tw.
13. exp Androgen Antagonists/
14. 1 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. (ae or po or to or co or de).fs.
16. exp Prostatic Neoplasms/
17. ((prostate or prostatic) and (cancer or carcinoma or adenocarcinoma or tumour or tumor or neoplasm$)).tw.
18. 16 or 17
19. 14 and 15 and 18
20. (safe or safety or side-effect of undesirable effect of treatment emergent or tolerability or toxicity or adrs).ti,ab.
21. (adverse adj2 (effect$ or reaction$ or event$ or outcome$)).tw.
22. 20 or 21
23. 14 and 18 and 22
24. 19 or 23

Embase 1974 to 2013 September 16
17th September 2013

1. (degarelix or firmagon or abarelix or plenaxis).tw.
2. degarelix/
3. abarelix/
4. exp gonadorelin/
5. exp hormone antagonist/
6. 4 and 5
7. ((luteinising or luteinizing or LHRH or gonadotrop$ or GNRH) and (agonist$ or antagonist$ or blocker$)).tw.
8. (androgen deprivation or ADT or androgen suppression).tw.
9. goserelin/
10. leuprorelin/
11. triptorelin/
12. buserelin/
13. buserelin acetate/

14. (goserelin or zoladex or novgos or eulexin or leuprorelin or leuprolide or prostap or lupron or eligard or carcinil or depo-eligard enanton or enantone or ginecrin or leuplin or lucrin or procren or procrin or trenantone or uno-enantone or viadur or triptorelin or trelstar or decapeptyl or gonapeptyl or salvacyl or buserelin or suprefact or suprecur or etilamide or bigonist or profact or receptal or flakon or cinnafact).tw.
15. bicalutamide/
16. (bicalutamide or casodex or cosudex or calutide or kalumid or bicalox).tw.
17. 1 or 2 or 3 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. (safe or safety or side-effect of undesirable effect of treatment emergent or tolerability or toxicity or adrs).ti,ab.
19. (adverse adj2 (effect$ or reaction$ or event$ or outcome$)).ti,ab.
20. 18 or 19
21. 17 and 20
22. degarelix/ae, to
23. abarelix/ae, to
24. exp gonadorelin/ae, to
25. exp hormone antagonist/ae, to
26. 24 and 25
27. goserelin/ae, to
28. leuprorelin/ae, to
29. triptorelin/ae, to
30. buserelin/ae, to
31. buserelin acetate/ae, to
32. bicalutamide/ae, to
33. or/22-23,26-32
34. 17 and 33
35. 21 or 34

Cochrane Library (Wiley Online)
13th September 2013

#1	degarelix or firmagon or abarelix or plenaxis:ti,ab,kw
#2	MeSH descriptor: [Gonadotropin-Releasing Hormone] explode all trees
#3	MeSH descriptor: [Hormone Antagonists] explode all trees
#4	(luteinising or luteinizing or LHRH or gonadotrop* or GNRH) and (agonist* or antagonist* or blocker*):ti,ab,kw
#5	(androgen deprivation or ADT or androgen suppression):ti,ab,kw
#6	MeSH descriptor: [Goserelin] this term only
#7	MeSH descriptor: [Leuprolide] this term only
#8	MeSH descriptor: [Triptorelin Pamoate] this term only
#9	MeSH descriptor: [Buserelin] this term only
#10	(goserelin or Zoladex or Novgos or Eulexin or leuprorelin or leuprolide or Prostap or Lupron or Eligard or Carcinil or Depo-Eligard Enanton or Enantone or Ginecrin or Leuplin or Lucrin or Procren or Procrin or Trenantone or Uno-Enantone or Viadur or triptorelin or Trelstar or Decapeptyl or Gonapeptyl or salvacyl or buserelin or Suprefact or suprecur or Etilamide or Bigonist or Profact or Receptal or Flakon or Cinnafact):ti,ab,kw
#11	(bicalutamide or Casodex or Cosudex or Calutide or Kalumid or Bicalox):ti,ab,kw
#12	MeSH descriptor: [Androgen Antagonists] explode all trees
#13	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
#14	MeSH descriptor: [Prostatic Neoplasms] this term only
#15	(prostate or prostatic) and (cancer or carcinoma or adenocarcinoma or tumour or tumor or neoplasm*):ti,ab,kw
#16	#14 or #15

#17 #13 and #16
#18 (safe or safety or side-effect of undesirable effect of treatment emergent or tolerability or toxicity or adrs):ti,ab
#19 (adverse next/2 (effect* or reaction* or event* or outcome*)):ti,ab,kw
#20 #18 or #19
#21 #17 and #20
#22 Any MeSH descriptor with qualifier(s): [Adverse effects - AE]
#23 Any MeSH descriptor with qualifier(s): [Drug effects - DE]
#24 Any MeSH descriptor with qualifier(s): [Chemically induced - CI]
#25 Any MeSH descriptor with qualifier(s): [Complications - CO]
#26 Any MeSH descriptor with qualifier(s): [Poisoning - PO]
#27 Any MeSH descriptor with qualifier(s): [Toxicity - TO]
#28 #22 or #23 or #24 or #25 or #26 or #27
#29 #17 and #28
#30 #21 or #29

Web of Science (Thomson Reuters)
17th September 2013

14 #13 AND #10
13 #12 OR #11
12 TS=((adverse NEAR/2 (effect* or reaction* or event* or outcome*)))
11 Topic=((safe or safety or side-effect of undesirable effect of treatment emergent or tolerability or toxicity or adrs))
10 #9 AND #8
9 Topic=(((prostate or prostatic) and (cancer or carcinoma or adenocarcinoma or tumour or tumor or neoplasm*)))
8 #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
7 Topic=(androgen antagonist*)
6 Topic=((bicalutamide or casodex or cosudex or calutide or kalumid or bicalox))
5 Topic=((goserelin OR zoladex) OR novos) OR eulexin) OR leuprorelin) OR leuprolide) OR prosta) OR lupron) OR eligard) OR carcini) OR depo-eligard enanton) OR enantone) OR ginecrin) OR leuplin) OR lucrin) OR procren) OR procain) OR trenantone) OR uno-enantone) OR vitadur) OR triptorelin) OR telstar) OR decapeptyl) OR gonapeptyl) OR salvacyl) OR buserelin) OR superfast) OR suprecur) OR ethylamide) OR bigonist) OR proact) OR receptal) OR flavon) OR cinnafact)
4 Topic=((goserelin or zoladex or novgos or eulexin or leuprorelin or leuprolide or prostap or lupron or eligard or carcinil or depo-eligard enanton or enantone or ginecrin or leuplin or lucrin or procren or procrin or trenantone or uno-enantone or viadur or triptorelin or trelstar or decapeptyl or gonapeptyl or salvacyl or buserelin or suprefact or suprecur or etilamide or bigonist or profact or receptal or flakon or cinnafact))
3 Topic=((androgen deprivation or ADT or androgen suppression))
2 Topic=(((luteinising or luteinizing or LHRH or gonadotrop* or GNRH) and (agonist* or antagonist* or blocker*)))
1 Topic=((degarelix or firmagon or abarelix or plenaxis))
4 Topic=((androgen deprivation or ADT or androgen suppression))
3 Topic=(((luteinising or luteinizing or LHRH or gonadotrop* or GNRH) and (agonist* or antagonist* or blocker*)))
2 Topic=(((degarelix OR firmagon) OR abarelix) OR planaxis)
1 Topic=((degarelix or firmagon or abarelix or plenaxis))

Appendix 5

ERG base case detailed results

Costs	Degarelix	Triptorelin 3 Monthly (Decapeptyl)	Incremental
Drug cost - flare cover	£0	£3	-£3
Drug cost - agonist or antagonist	£12,471	£6,463	£6,008
Administration cost during 1st line treatment	£1,919	£1,368	£551
Drug cost - anti-androgens (anti-androgen addition)	£19	£20	-£1
Administration cost during anti-androgen addition	£237	£231	£6
Administration cost during anti-androgen withdrawal	£223	£216	£7
Drug cost - chemotherapy	£121	£128	-£7
Administration and side effect cost during 1st line chemotherapy	£945	£968	-£23
Drug cost - abiraterone	£3,173	£3,341	-£168
Administration and concomitant medications cost during treatment with	£384	£394	-£10
Cost of follow-on treatment after abiraterone	£440	£318	£121
Cost of supportive care	£4,198	£4,208	-£9
Cost of palliative care	£1,280	£1,286	-£6
Cost of SCC	£0	£1,863	-£1,863
Cost of fractures	£120	£1,012	-£892
Cost of joint related signs and symptoms	£124	£182	-£58
Cost of CV events	£655	£647	£8
Total Costs	**£26,308**	**£22,649**	**£3,659**

Costs	Degarelix	Triptorelin 3 Monthly (Decapeptyl)	Incremental
1st line treatment	£9,720	£5,193	£4,527
Anti-androgen addition	£627	£460	£167
Anti-androgen withdrawal	£574	£414	£160
Chemotherapy	£1,105	£1,118	-£13
Abiraterone	£3,707	£3,820	-£113
Supportive and palliative care	£9,677	£7,940	£1,737
Adverse events	£899	£3,704	-£2,805
Total Costs	**£26,308**	**£22,649**	**£3,659**

QALYs	Degarelix	Triptorelin 3 Monthly (Decapeptyl)	Incremental
1st line treatment	4.03	3.70	0.33
Anti-androgen addition	0.17	0.17	-0.01
Anti-androgen withdrawal	0.16	0.16	-0.01
Chemotherapy	0.18	0.18	-0.01
Abiraterone	0.06	0.06	0.00
Supportive and palliative care	1.23	1.29	-0.06
Total QALYs	**5.82**	**5.57**	**0.25**

Life Years	Degarelix	Triptorelin 3 Monthly (Decapeptyl)	Incremental
1st line treatment	5.39	5.03	0.36
Anti-androgen addition	0.26	0.27	-0.01
Anti-androgen withdrawal	0.25	0.26	-0.01
Chemotherapy	0.32	0.33	-0.01
Abiraterone	0.11	0.11	0.00
Supportive and palliative care	3.23	3.39	-0.16
Total Life Years	**9.55**	**9.39**	**0.16**

Appendix 6 Details of the methods used to run ERG additional analyses

ERG Analysis	Methods used
ERG base case: 3-monthly triptorelin , LHRH agonists and degarelix administered until death , One year duration for which the hazard ratio for differential efficacy applied , The proportion of patients receiving chemotherapy after PSA progression was 70% and the proportion of patients receiving abiraterone was 70%	The variable p_1stlinecomparator was changed.The variable ctrl_costing_continuation was changed. The variable p_1stline_effic_assumption was changed.The variables ctrl_prop_noDocetaxel and ctrl_prop_noAbiraterone were changed.
· Patient age of 65 years	The variable p_avg_age was changed.
· Patient age 80 years	The variable p_avg_age was changed.
· An exploratory analysis in which SCC adverse events are excluded from the analysis.	The proportion experiencing SCC in E171 on Parameters sheet was set to zero.
· 6 monthly Triptorelin (the cheapest of all the LHRH agonists)	The variable p_1stlinecomparator was changed.
· An exploratory analysis which assumes that the rate of fractures is the same for both the degarelix and LHRH agonist arms. (The Weibull curve in the MS for LHRH agonists was used for both arms.)	The values in cells P15 and P16 were set to match those in cells T15 and T16 on sheet 'Adverse Event Curves'.
· Variations in treatment pathway: an analysis in which the proportion of patients receiving chemotherapy after PSA progression was reduced to 40% and the proportion of patients receiving abiraterone was reduced to 40%	The variables ctrl_prop_noDocetaxel and ctrl_prop_noAbiraterone were changed.
· Metastatic patients who progress from first-line treatment have no increased risk of mortality. The evidence linking PSA progression and overall survival is inconclusive.	The variable inc_PSAmeta_mortality was changed.
· Efficacy of degarelix and LHRH agonists assumed to be equal.	The variable p_1stline_effic_assumption was changed.

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