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 dose schedules of degarelix (3-monthly or intermittent), 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 used an unlicensed 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

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). Although a comprehensive list of free-text terms were employed, it should be noted that mapping to subject headings combined with free-text terms is needed to achieve optimal retrieval (recall and precision). However, due to time restrictions the ERG could not confirm if studies for indirect comparison have been missed.

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 uses a 3-monthly dosing regimen of degarelix versus a 3-monthly dosing regimen 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.

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 (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.

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, sufficient justification has not 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.

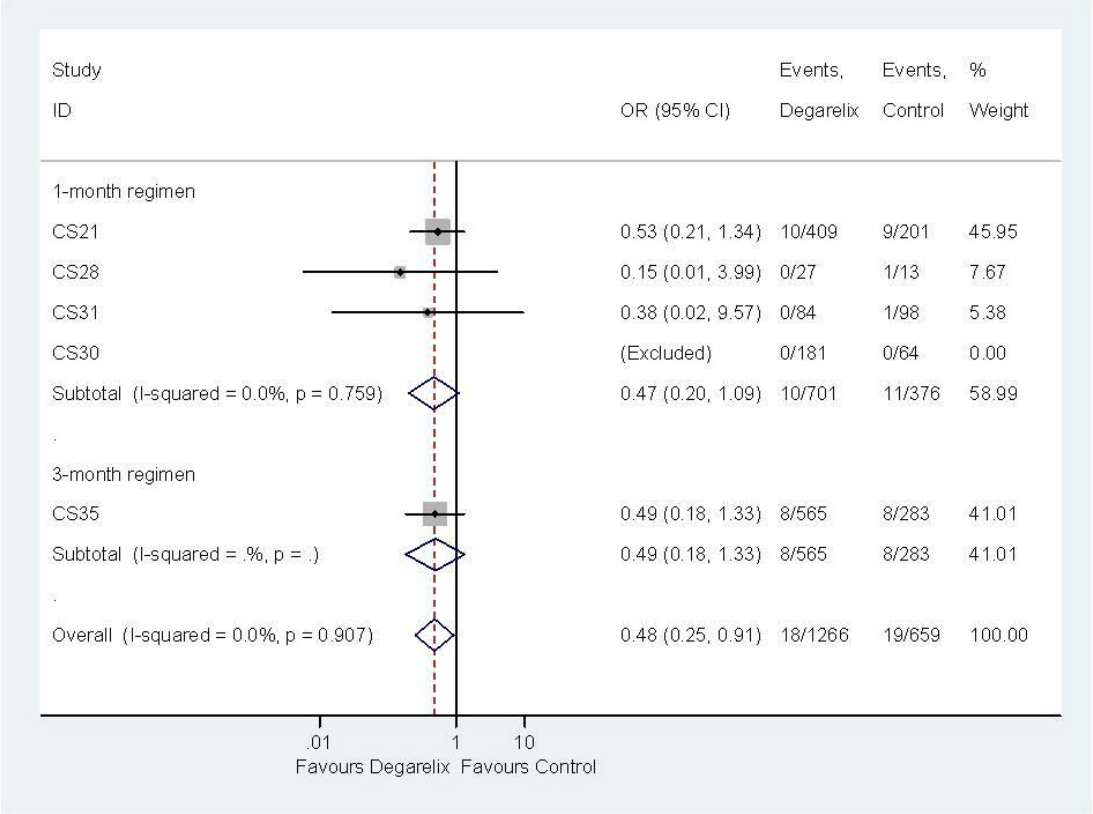
Additionally the manufacturer reports the mean differences between the treatment groups have been used for this meta-analysis rather than the median values "*as the differences between degarelix and the LHRH agonists were symmetrically distributed*" (MS page 76) but the median PSA values were used when 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.

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:

- Sufficient justification has not 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 intermittent dosing regimen 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).

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 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

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)[29] suggests PSA progression is inappropriate as a surrogate endpoint in castration-resistant cancer patients[29] 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.

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 corrected model included within the manufacturer's response to clarifications.

Table 41: Deterministic model results for sensitivity analyses on parameter values (replicated from MS Clarification Appendix 9 Table 8)

Parameter	Base case	Sensitivity analysis	ICER	Incremental net benefit (threshold £20,000)
Base case	N/A	N/A	Dominating	£13,296
Varying the comparator				
First-line LHRH agonist	Goserelin 10.8mg (Zoladex)	Goserelin 3.6 mg (Novgos)	Dominating	£12,682
		Goserelin 3.6 mg (Zoladex)	Dominating	£13,012
		Leuprorelin 3.75mg (Prostap)	Dominating	£13,532
		Leuprorelin 11.25mg (Prostap)	Dominating	£13,139
		Triptorelin 3.75 mg (Gonapeptyl)	Dominating	£13,860
		Triptorelin 3mg (Decapeptyl)	Dominating	£13,215
		Triptorelin 11.25mg (Decapeptyl)	Dominating	£12,822
		Triptorelin 22.5mg (Decapeptyl)	Dominating	£14,484
Varying treatment efficacy assumptions				
Variation of the parametric curve chosen				
Curve choice for first-line time to PSA progression	Log-normal	Log-logistic	Dominating	£13,140
		Gompertz	Dominating	£13,256
		Exponential	Dominating	£12,798
		Weibull	Dominating	£12,342
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	£11,274	£1,031
		For one year; the duration for which there is comparative trial data	£3,061	£4,161
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	£11,683
	ii) Prostate cancer specific mortality incorporated	i) No increased hazard of mortality post-progression for metastatic patients ii) General population mortality incorporated	Dominating	£16,976
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	Include no MSEs	£2,152	£8,853
		Include all MSEs[a]	Dominating	£13,114

	compression incorporated in the model			
Variation in the parametric curve used to model MSEs over time				
Parametric curve for MSEs	Weibull	Exponential	Dominating	£13,371
Variation of proportion of mild, moderate and severe MSEs across both arms				
Proportion of Mild, Moderate and Severe MSEs	Equal across both arms	Proportions as seen in trial	Dominating	£13,386
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	£13,031
Curve choice for CV event	Exponential	Weibull	Dominating	£13,386
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	£11,469
		i) Gray Algorithm[d] ii) Gray Algorithm[4] iii) Sourced from systematic search iv) Gray Algorithm[d]	Dominating	£9,311
		i) Rowen Algorithm[e] ii) Rowen Algorithm[e] iii) Sourced from systematic search iv) Rowen Algorithm[e]	Dominating	£12,458
		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	£15,291
Variation in treatment and administration practice				
Treatment used for flare cover and anti-androgen	Bicalutamide	Cyproterone acetate	Dominating	£13,329

addition				
Treatment with LHRH and degarelix takes place in	50% primary care; 50% secondary care	All treated in primary care	Dominating	£13,223
		All treated in secondary care	Dominating	£13,368
Incorporation of abiraterone	Incorporated in the treatment pathway	Not incorporated	£2,089	£10,627
Stopping rule	Stop treatment on degarelix/ LHRH agonist when castrate/ resistant, in line with the licensed indication	Don't stop treatment until death	Dominating	£12,312
Varying the time horizon				
Time horizon	30 Years	5 years	Dominating	£5,068
		10 Years	Dominating	£10,010
		20 Years	Dominating	£13,194

[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 which used updated distributions following the clarification process 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.

9. REFERENCES

1. National Institute for Health and Care Excellence. Tumour Node Metastasis (TNM) clinical staging classification of prostate cancer. 2013; available from http://cks.nice.org.uk/prostate-cancer#!backgroundsub:8 (accessed Oct. 2013).

2. National Institute for Health and Care Excellence. Prostate cancer: diagnosis and treatment. *NICE Clinical Guideline CG58* 2008. Cardiff, National Collaborating Centre for Cancer.

3. Office for National Statistics. Statistical bulletin: Cancer incidence and mortality in the United Kingdom 2008-2010. ONS, editor. 2012.

4. BAUS. The British Association of Urological Surgeons: Section of Oncology. *Analyses of Complex operations and the Newly diagnosed registry for Urological cancers January 1st – 31st December 2010*. 2011.

5. Public health England, S.W.P.H.O. Treatment routes in prostate cancer (2010 data). 2013.

6. Tombal, B., Miller, K., Boccon-Gibod, L., SchrÃ¶der, F., Olesen, T.K., Persson, B.E. Degarelix versus leuprolide in prostate cancer patients: new prostate-specific antigen data from a phase III trial (CS21). *EJC Supplements* 2009; 7(2):411.

7. Europen Medicines Agency. European Public Assessment Report (EPAR) Firmagon EPAR summary for the public . *European Medicines Agency*, 2009.

8. Scottish Medicines Consortium. Degarelix 120mg and 80mg powder and solvent for solution for injection (Firmagon®). *Scottish Medicines Consortium* 2010; SMC No.(560/09).

9. All Wales Medicines Strategy Group . All Wales Medicines Strategy Group Final Appraisal Recommendation – 4112: Degarelix (Firmagon®) 80 mg and 120 mg injection November 2012. *AWMSG* 2012.

10. Iversen, P., Tyrrell, C.J., Kaisary, A.V., Anderson, J.B., Baert, L., Tammela, T. et al. Casodex (bicalutamide) 150-mg monotherapy compared with castration in patients with previously untreated nonmetastatic prostate cancer: results from two multicenter randomized trials at a median follow-up of 4 years. *Urology* 1998; 51(3):389-396.

11. Tyrrell, C.J., Kaisary, A.V., Iversen, P., Anderson, J.B., Baert, L., Tammela, T. et al. A randomised comparison of ΓÇÿCasodexΓÇÖTM (bicalutamide) 150 mg monotherapy versus castration in the treatment of metastatic and locally advanced prostate cancer. *European Urology* 1998; 33(5):447-456.

12. Iversen, P., Damber, J., Malmberg, A., Persson, B., Klotz, L.
Improved outcomes with degarelix monotherapy compared with luteinizing hormone-releasing hormone (LHRH) agonists plus antiandrogen flare protection in the treatment of men with advanced prostate cancer. *29th Congress of the Scandinavian Association of Urologists* 2013.

13. Conteduca, V., Di Lorenzo, G., Tartarone, A., Aieta, M. The cardiovascular risk of gonadotropin releasing hormone agonists in men with prostate cancer: An unresolved controversy. *Critical Reviews in Oncology/Hematology* 2012.

14. Jespersen, C.G., N+©rgaard, M., Borre, M. Androgen-deprivation Therapy in Treatment of Prostate Cancer and Risk of Myocardial Infarction and Stroke: A Nationwide Danish Population-based Cohort Study. *European Urology* 2013.

15. Klotz, L., Boccon-Gibod, L., Shore, N.D., Andrreou, C., Persson, B.-E., Cantor, P. et al. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. *BJU International* 2008; 102:1531-1538.

16. Anderson, J., Al-Ali, G., Wirth, M., Gual, J.B., Gomez, V.F., Colli, E. et al. Degarelix versus Goserelin (+ Antiandrogen Flare Protection) in the relief of lower urinary tract symptoms secondary to prostate cancer: results from a phase IIIb study (NCT00831233). *Urologia Internationalis* 2013; 90(3):321-328.

17. Mason, M., Maldonado, P., X, Steidle, C., Guerif, S., Wiegel, T., van der Meulen, E. et al. Neoadjuvant androgen deprivation therapy for prostate volume reduction, lower urinary tract symptom relief and quality of life improvement in men with intermediate- to high-risk prostate cancer: a randomised non-inferiority trial of degarelix versus goserelin plus bicalutamide. *Clinical Oncology (Royal College of Radiologists)* 2013; 25(3):190-196.

18. Axcrona, K., Aaltomaa, S., da Silva, C.M., Ozen, H., Damber, J.E., Tanko, L.B. et al. Androgen deprivation therapy for volume reduction, lower urinary tract symptom relief and quality of life improvement in patients with prostate cancer: degarelix vs goserelin plus bicalutamide. *BJU Int* 2012; 110(11):1721-1728.

19. Doshi, P., Jefferson, T. Clinical study reports of randomised controlled trials: an exploratory review of previously confidential industry reports. *BMJ Open* 2013; 3(2).

20. Klotz, L., Miller, M., Crawford, D., Shore, N., Tombal, B., Karup, C. et al. Analysis of disease-control outcomes from five comparative randomised clinical trials of degarelix versus luteinising hormone-releasing hormone agonists. *European Urology* 2013; Submitted.

21. Ameringer, S., Serlin, R.C., Ward, S. Simpson's paradox and experimental research. *Nursing Research* 2009; 58(2):123.

22. Lievre, M., Cucherat, M., Leizorovicz, A. Current Controlled Trials in Cardiovascular Medicine. *Current Controlled Trials in Cardiovascular Medicine* 2002; 3:6.

23. Bravata, D.M., Olkin, I. Simple pooling versus combining in meta-analysis. *Evaluation & the Health Professions* 2001; 24(2):218-230.

24. Borenstein, M., Hedges, L.V., Higgins, J.P., Rothstein, H.R. Introduction to meta-analysis. Wiley. com, 2011.

25. Chan, W.K., Redelmeier, D.A. Simpson's paradox and the association between vitamin D deficiency and increased heart disease. *The American Journal of Cardiology* 2012; 110(1):143-144.

26. Tombal, B., Miller, K., Boccon-Gibod, L., Schroder, F., Shore, N., Crawford, E.D. et al. Additional analysis of the secondary end point of biochemical recurrence rate in a phase 3 trial (CS21) comparing degarelix 80 mg versus leuprolide in prostate cancer patients segmented by baseline characteristics. *Eur Urol* 2010; 57(5):836-842.

27. Bourke, L., Kirkbride, P., Hooper, R., Rosario, A.J., Chico, T.J., Rosario, D.J. et al. Endocrine therapy in prostate cancer: time for reappraisal of risks, benefits and cost-effectiveness?. [Review]. *British Journal of Cancer* 2013; 108(1):9-13.

28. Schroder, F.H., Tombal, B., Miller, K., Boccon-Gibod, L., Shore, N.D., Crawford, E.D. et al. Changes in alkaline phosphatase levels in patients with prostate cancer receiving degarelix or leuprolide: results from a 12-month, comparative, phase III study. *BJU Int* 2010; 106(2):182-187.

29. Scher, H.I., Morris, M.J., Larson, S., Heller, G. Validation and clinical utility of prostate cancer biomarkers. *Nature Reviews Clinical Oncology* 2013; 10(4):225-234.

30. Lakhal, L., Rivest, L.P., Beaudoin, D. IPCW estimator for Kendall's Tau under bivariate censoring. *The International Journal of Biostatistics* 2009; 5(1).

31. BMJ group. Study design search filters: Clinical Evidence BMJ. 2013; available from http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html (accessed Oct. 2013).

32. Ozono, S., Ueda, T., Hoshi, S., Yamaguchi, A., Maeda, H., Fukuyama, Y. et al. The efficacy and safety of degarelix, a GnRH antagonist: a 12-month, multicentre, randomized, maintenance dose-finding phase II study in Japanese patients with prostate cancer. *Jpn J Clin Oncol* 2012; 42(6):477-484.

33. Crawford, E.D., Tombal, B., Miller, K., Boccon-Gibod, L., Schroder, F., Shore, N. et al. A phase III extension trial with a 1-arm crossover from leuprolide to degarelix: comparison of gonadotropin-releasing hormone agonist and antagonist effect on prostate cancer. *J Urol* 2011; 186(3):889-897.

34. Geiges, G., Tolle, A., Schulze, M., Gedamke, M. Alkaline Phosphatase Control And Prostate Volume Reduction Under Degarelix Treatment In Prostate Cancer Patients Confirmed By Real Life Data From A German Registry. *The Journal of urology* 2012; 187[4S], e309.

35. Ades, A.E., Caldwell, D.M., Reken, S., Welton, N.J., Sutton, A.J., Dias, S. NICE DSU Technical Support Document 7: Evidence Synthesis Of Treatment Efficacy In Decision Making: A Reviewers Checklist. *Available Fr Om Http://Www Nicedsu Org Uk* 2012.

36. Seidenfeld, J., Samson, D.J., Hasselblad, V., Aronson, N., Albertsen, P.C., Bennett, C.L. et al. Single-therapy androgen suppression in men with advanced prostate cancera systematic review and meta-analysis. *Annals of Internal Medicine* 2000; 132(7):566-577.

37. Heyns, C.F., Simonin, M., Grosgurin, P., Schall, R., Porchet, H.C. Comparative efficacy of triptorelin pamoate and leuprolide acetate in men with advanced prostate cancer. *BJU International* 2003; 92(3):226-231.

38. Lu, L., Peters, J., Roome, C., Stein, K. CostΓÇÉeffectiveness analysis of degarelix for advanced hormoneΓÇÉdependent prostate cancer. *BJU International* 2012; 109(8):1183-1192.

39. The cost effectiveness of degarelix for the treatment of prostate. Cancer in the UK. 2011.

40. Hatoum, H.T., Crawford, E.D., Nielsen, S.K., Lin, S.J., Marshall, D.C., Hatoum, H.T. et al. Cost-effectiveness analysis comparing degarelix with leuprolide in hormonal therapy for patients with locally advanced prostate cancer. *Expert Review of Pharmacoeconomics & Outcomes Research* 2013; 13(2):261-270.

41. Hatoum, H.T., Crawford, E.D., Nielsen, S.K., Lin, S.J., Marshall, D.C., Hatoum, H.T. et al. Cost-effectiveness analysis comparing degarelix with leuprolide in hormonal therapy for patients with locally advanced prostate cancer. *Expert Review of Pharmacoeconomics & Outcomes Research* 2013; 13(2):261-270.

42. British National Formulary. *British National Formulary* 2013.

43. Hussain, M., Goldman, B., Tangen, C., Higano, C.S., Petrylak, D.P., Wilding, G. et al. Prostate-specific antigen progression predicts overall survival in patients with metastatic prostate cancer: data from Southwest Oncology Group Trials 9346 (Intergroup Study 0162) and 9916. *Journal of Clinical Oncology* 2009; 27(15):2450-2456.

44. Oh, W.K., Landrum, M.B., Lamont, E.B., McNeil, B.J., Keating, N.L. Does Oral Antiandrogen Use Before Leuteinizing Hormone-releasing Hormone Therapy in Patients With Metastatic Prostate Cancer Prevent Clinical Consequences of a Testosterone Flare? *Urology* 2010; 75(3):642-647.