Brief Critique on Additional Evidence presented in the Manufacturer's Response to the NICE Appraisal Consultation Document for Degarelix for Advanced Hormone-Dependent Prostate Cancer [ID590]

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Abbreviations

ACD- Appraisal consultation document
AIC- Akaike information criterion
BIC- Bayesian Information criterion
CSR- Clinical study report
CVD- Cardiovascular disease
FAS- Full analysis set
FSH- Follicle-stimulating hormone
HR- Hazard ratio
JSS- Joint related signs and symptoms
MR- Manufacturer's response (to the ACD) including the letter of address; Appendix A and revised model (4th February 2014)
MS- Manufacturer's submission (29th August 2013)
PSA- Prostate specific antigen
PSA*- Probabilistic sensitivity analysis
SAE- Serious adverse events

SMQ- Standardised MedDRA queries

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Executive Summary

The Evidence Review Group (ERG) has reviewed the manufacturer's response (MR) to the Appraisal Consultation Document (ACD); the meta-regression analyses and the revised model. A brief critique of this additional evidence has been undertaken by the ERG and is presented in this document. The manufacturer has presented evidence which aims to demonstrate that degarelix may offer superior benefit to comparators for patients with high risk of Prostate Specific Antigen (PSA) progression and/or pre-existing cardiovascular disease.

The main comments of the ERG regarding the clinical evidence presented in the MR:

- The manufacturer asserts that potential underlying mechanisms suggested from observational studies lends weight to causal conclusions inferred from the manufacturer's correlative findings. Direct evidence of the proposed underlying mechanisms is required to corroborate these assumptions.

- The claim that the CS21A trial supports the significant PSA progression free survival (PFS) benefit for degarelix over leuprorelin is erroneous. The extension trial cannot claim to support a superior benefit of degarelix when there was no leuprorelin treatment arm in this extension study.

- The use of a non-stratified one step fixed effects meta-regression is not justified. A reference by Tudur Smith *et al* (2007) is wrongly cited as this study uses a stratified, not a non-stratified, approach. A stratified model may be preferred since it preserves the randomisation within each study. The manufacturer states that due to software limitations a fixed effects model was chosen. However, a random effects model can be analysed using S-*Plus* and *R* software. A random effects analysis is likely to produce more uncertainty, and therefore, less favourable results than the fixed effects analysis employed.

- The inclusion of trial CS35, which uses an unlicensed dose of degarelix in the fixed effects analysis, is inappropriate.

- Trial heterogeneity has not been sufficiently explored and reported. The meta-regression analyses adjusted for several covariates and subsequently the manufacturer concludes that "no heterogeneity" was found. Tests for heterogeneity should include the heterogeneity term only. Although, the manufacturer has performed meta-regression, it is still not clear if the studies included in the meta-analysis were homogeneous.

- The additional analyses use a frequentist approach and hence assume that the estimated parameters are normally distributed in the probability sensitivity analysis (PSA*). The manufacturer does not consider the potential advantages of using a Bayesian approach. Subsequently parametric distributions were fitted to pooled data, where it is not clear that if all included studies were homogeneous.

- There is tenuous evidence for the claim of a significant PSA PFS for degarelix. Whilst the adjusted HR from the meta-regression of trials CS21 and CS35 for PSA PFS are significant [redacted] results from the meta-regression of PSA PFS of trials CS21 and CS35 (all doses) for the PSA > 20ng/mL subgroup (FAS) are no longer

significant [redacted] Additionally results from the meta-regression of PSA PFS of trials CS21 and CS35 (all doses) for the locally advanced and metastatic FAS [redacted] Moreover, it is not clear whether trials CS21 and CS35 used the same definition of PSA PFS.

- The claim that the benefits of degarelix will be "roughly equivalent or greater" in the PSA>20ng/ml subgroup than the observed HR of [redacted] is misleading as the manufacturer had already adjusted for baseline risk in this analysis.

- The hazard ratio of the CV SAE profile is a more plausible value in terms of being statistically significant. However, when compared to the results of the individual trials which make up the pooled result in the appendices, the pooled result is implausible. The pooled results in the appendices have more favourable p-values than the individual trials (Tables 2.1; 2.2; 2.3; 2.4; 2.5; 2.7; 2.8 in Appendix B). This is likely to be a result of using the fixed effects model which assumes the treatment effect is the same and that with each estimate precision is increasing.

- For the meta-regression curves (MR Figure A3) it is unclear whether the two degarelix arms (80mg & 160mg) in the CS21 trial have been pooled or whether just the licensed dose arm has been selected for this analysis.

The main comments of the ERG on the economic evidence presented in the MR:

- The use of an alternative utilities algorithm; the continuation of first-line hormonal therapy until death; and the provision of additional scenario analyses are useful changes to the economic model.

- The meta-regression analyses used within the economic model are associated with serious limitations.

- The use of drug cost of a blended comparator is not an appropriate update to the model.

- The inclusion of enzalutamide is inappropriate as it is not consistent with the current NICE ACD2 for enzalutamide.

- There are some errors in the MR model and the results for the subgroup with pre-existing CVD are not presented.

- The ERG considers that the results presented in the ACD are the most appropriate for consideration.

Evidence Review Group Brief Critique

The ERG has retained the headings used by Ferring in the letter of address for the Manufacturer's Response (MR) in order to facilitate cross-referencing to the manufacturer's specific premises for responding to the ACD.

1. **PSA progression**

a. Mechanism of action

Manufacturer's premise *"further clarification of the differential mechanism of action of degarelix, versus luteinising hormone-releasing hormone (LHRH) agonists, and the subsequent impact this is likely to have on PSA progression"*

As stated by the manufacturer, the mechanism of action which may account for the observed and reported benefits is not fully established. Therefore two hypotheses are proposed in the MR. Firstly that breakthrough increases in testosterone can adversely affect progression free survival (PFS). The authors cite a paper (Morote *et al* 2007) in which a correlation was found in 73 patients between breakthrough testosterone increases and a lower androgen independent progression. The paper concludes that "*observations in the report imply that, at least for the highest and classic range of testosterone of 50 ng/dl, maximal androgen blockade (by adding bicalutamide to LH-RH agonist) might have a beneficial role*". The ERG considers that a correlative study of 73 patients does not represent sufficient evidence to support this hypothesis for the underlying mechanism of action of degarelix.

A second hypothesis proposed by the manufacturer is that LHRH agonists have poorer long-term FSH control than degarelix. One reference is cited supporting the finding that "FSH receptor is selectively expressed on the surface of the blood vessels of a wide range of tumors (Radu *et al* 2010). Additionally a study is cited which supports the role of FSH in the pathogenesis and progression of prostate cancer (Porter *et al* 2001). Evidence to support the reduction of FSH from treatment with degarelix comes from the Van Poppel *et al* (2008) study. Additionally the Klotz *et al* (2008) study is cited which concluded from trial CS21 that there was a "*more rapid decrease in FSH after degarelix treatment, and the FSH levels did not fall to the same extent with leuprolide"*. As this evidence is versus leuprorelin only it is not possible to extend the reported benefit of degarelix on FSH control to all LHRH agonists. Additionally, direct evidence linking the potential role of a rapid decrease in FSH with PSA progression is lacking.

b. Efficacy data: CS21A extension study

Manufacturer's premise *"restates the pivotal findings of the Phase III extension trial (CS21A), which support the statistically significant PSA PFS benefit for degarelix over leuprorelin seen during the first year of treatment.*[3,4]*"*

This is a reiteration of evidence from the MS. Crawford *et al* (2011) and Crawford *et al* (2014; in press) are cited however the latter paper is not provided. In the CS21A extension trial (Crawford *et al* 2011) those who switched from leuprorelin to degarelix had a significantly reduced hazard rate for PFS PSA whilst those who continued with degarelix were reported to remain consistent. This was not a trial of degarelix versus leuprorelin. Therefore the manufacturer's claim that "*These results from the crossover population in the CS21A extension study clearly show that degarelix is providing an improved, differential effect in terms of PSA PFS compared with leuprorelin in the longer term*" cannot be substantiated. It is a single arm crossover trial (with two degarelix dosing regimens) in

which all patients received degarelix. As described in the ERG report (page 63) the hazard rate was not entirely consistent as those who switched had a lower (but not significant) hazard rate. Also the patients who entered the extension trial were not randomly allocated to the trial and therefore there is no guarantee that the 385 patients who entered the extension trial are similarly balanced to or fully representative of the 504 patients who entered the CS21 trial.

2. Cardiovascular data

a. Peer-reviewed, independent evidence of the CV risk benefit of degarelix

Manufacturer's premise: "*the reduced risk of cardiovascular (CV) serious adverse events (SAEs) and death in patients with CV disease (CVD) at baseline in those treated with degarelix versus LHRH agonists. Ferring would like to take this opportunity to reiterate the relevance of the recent, independently produced, peer-reviewed publication by Albertsen et al 2013.*[5] *The conclusions of this paper present the full impact and clinical importance of the reduced risk of CV SAEs and death of degarelix versus LHRH agonists."*

The manufacturer claims that there is a reduced risk of CV SAEs in people with pre-existing CVD for patients treated with degarelix versus patients treated with LHRH agonists. This is a causal inference from a post hoc observation based on simple pooling of heterogeneous trials. CV SAEs were not a pre-defined clinical endpoint but were adverse events which have been collected from post hoc inspection of the data. In the analysis presented in the Albertsen *et al* (2013) paper, the only study not to cross the line of no effect in this analysis was the CS37 intermittent degarelix trial (Fig. 3 of Albertsen *et al* 2013). The HRs for CV events in the other 2 trials are equivocal. The difference only pertains to the subgroup of men with pre-existing CVD in the Albertsen *et al* (2013) publication (and in the MR). No effect has been demonstrated in men without pre-existing CVD. Again the manufacturer claims that there is "no sign of trial heterogeneity". Whilst "no heterogeneity" is reported there was almost certainly clinical heterogeneity due to the different dosing regimens and inclusion criteria of the included trials.

b. Meta-regression analysis of CV data

Manufacturer's premise: *"the requested meta-regression analysis that evaluates the risk of CV SAEs and death in patients with pre-existing CVD is presented. This analysis demonstrates that there is no sign of trial heterogeneity and adjusted hazard ratios are used in the updated economic model. The results show that among men with pre-existing CVD, the risk of CV SAEs (including death) within one year of initiating therapy was significantly lower for men treated with a degarelix compared with LHRH agonists* [redacted]. *The results are also significant when excluding death (*[redacted]. *These results are in line with those from the pooled analysis and Albertsen et al 2013*[5] *that formed part of the original submission."*

The aim of meta-regression is to investigate whether a particular covariate or characteristic, with a value defined for each trial in the meta-analysis, is related to the extent of the treatment benefit. In the MR individual patient-level data meta-regression was conducted using a one-step non-stratified fixed effects model assuming both fixed trial effects and fixed treatment effect. The non-stratified model assumes that the hazards within each trial are proportional to the same common baseline hazard function. However, this assumption may be inappropriate because of the different trial settings and

patient populations. Hence, a stratified model with a different baseline for each trial may be more suitable since it preserves the randomisation within each study. Furthermore, the manufacturer did not provide the correct reference to the meta-regression method used. The reference cited (Tudur-Smith *et al* 2007) only described the stratified fixed effects model.

The reason for using the fixed effects model given by the manufacturer was due to software for random effects models being at a developing stage. The ERG disputes the validity of this reason since both Smith *et al* (2005) and Bowden *et al* (2011) suggest that S-*Plus* and *R* software can be used. The use of the fixed effects model inappropriately leads to more precise pooled estimate than it really is. For example, in Table 2.8 (MR Appendix A), two of three included studies were not significant (CS21, p-value=[redacted] and CS35, p-value=[redacted]). In addition, the study which provided borderline significant results (CS37, p-value=[redacted]) was smaller than both non-significant trials. However, the pooled estimate of HR was highly significant (p-value=[redacted]). The analysis for all outcomes in these meta-regression analyses suffered a similar problem. The estimates would undoubtedly be less significant if a random effects model is used.

3. <u>Subgroups of greatest benefit</u>

a. <u>Pre-existing cardiovascular risk</u>
Manufacturer's premise: *"The significantly reduced CV and death risk that degarelix offers, compared with LHRH agonists, is of particular relevance to the decision problem, as the population covered by the licensed indication of degarelix has a high prevalence of CV co-morbidity"*

This is a restatement of evidence from the MS discussed on page 66 of ERG report. This relationship was drawn from a simple pooled analysis from post hoc data. The reduced CV SAE and death event highlighted in the MS and MR is a correlative relationship from a flawed analysis which has been ascribed a causal conclusion.

b. <u>Fractures and joint-related signs and symptoms</u>
Manufacturer's premise: "*Treatment with degarelix is no longer significant when compared with treatment with LHRH for fractures."*

The manufacturer correctly describes, as discussed in the AC meeting, that a "*a proportional hazards assumption is unlikely to hold due to the nature of fracture events in prostate cancer with disease-related events (pathological fractures) more likely to be experienced early on and osteoporotic fractures becoming more common with advanced age*" and that "*therefore, a single hazard ratio cannot be accurately calculated."* Additional scenario analyses to address this uncertainty are described in Section 7 (c) of this critique.

c. <u>The wider population</u>
Manufacturer's premise: *"that the initial focus on the immediate suppression benefit of degarelix to only those at risk of spinal cord compression (SCC) lent undue weight to discussions held during the AC meeting and a lack of credit or weight was placed on the other subgroups highlighted within the ACD; e.g., 'The clinical specialists also highlighted that*

degarelix is particularly appropriate for people at high risk of disease progression (that is, with a prostate-specific antigen [PSA] level of more than 20 ng/ml), for people with spinal metastases who are at risk of impending spinal cord compression, older people and those with pre-existing cardiovascular disease' [page 27, section 4.2]. Furthermore, whilst we note that the immediate suppression of testosterone offered by degarelix is of benefit to those at risk of SCC, this clinical efficacy characteristic is also of benefit to a wider population, i.e. all patients at risk of, or suffering from, symptomatic disease, including those with bone pain and/or bone metastases and/or bladder outlet obstruction (BOO)."

The potential benefits of degarelix to subgroups highlighted by clinical specialists are yet to be substantiated by direct evidence in the MS or the MR.

The manufacturer states that due to the greater underlying risk of progression in the high risk group (PSA>20 ng/ml) compared to the overall population this "*lead[s] to roughly equivalent or greater benefits from the use of degarelix to slow PSA progression*". The estimated HR for the PSA>20 ng/ml was already adjusted for baseline covariates which included Gleason score, disease stage and baseline PSA. Hence, the high risk group will not have equivalent or greater benefits by treating with degarelix on PSA PFS than the overall population and this statement is misleading.

4. Meta regression analyses

a. Requested meta-regression

Manufacturer's premise: *"we present within this response the following meta-regression analyses (i.e. the ERG requested meta-analyses) to re-confirm the efficacy and safety analysis results by adopting the preferred methodology from NICE/AC (see **Table 1**)."*

The statistically significant heterogeneity that was found in the meta-analysis for PSA response in the original MS was raised by the ERG as not being explored using formal meta-regression (ERG report page 81). However this was only one of the criticisms of the ERG, with the more pressing issue being the selective inclusion of trial CS35. The main concerns surrounding the clinical evidence in the MS which highlighted in the ERG report and/or discussed in the AC were:

- Only half of the trial population were locally advanced or metastatic.
- Baseline characteristics of the PSA>20ng/ml subgroup weren't provided.
- Trial CS35 is selectively included despite using an unlicensed dose of degarelix.
- Conclusions about statistically lower risks of fractures; joint-related signs and symptoms; and urinary tract events were drawn from simple pooled analyses.
- Comparators treated as clinically equivalent which was reliant on data from meta-analyses which did not include triptorelin.
- Conclusions drawn about overall survival from trials which were inadequately designed to capture meaningful differences in OS.
- Failure to explore evidence suggesting treatment effect of triptorelin may be different to leuprorelin and goserelin. The ERG's analyses showed triptorelin was associated with lower mortality than leuprorelin.
- No clear evidence that treatment effect was not dependent on stage of disease. Results showing patients receiving degarelix had a lower risk of PSA progression or death compared

with patients receiving leuprorelin (p=0.05), when adjusted for baseline PSA levels and disease stage were no longer statistically significant (HR 0.664 [95%CI 0.385 to 1.146].

Additionally the CS21 trial was a three-arm study with patients in two arms being treated with different doses of degarelix (160 or 80mg). It is not clear how these two arms were dealt with in the meta-regression i.e., whether just the licenced dose arm was used or whether both arms were pooled in the MR.

All the analyses excluded studies which did not contribute with events in one or both arms. It is appropriate to exclude studies with no events in both arms. However, it is inappropriate to exclude studies with no events in one arm. This approach discarded some of the evidence, which could inform the pooled estimates.

b. Assessment of trial heterogeneity using individual patient data

Manufacturer's premise: "*As detailed within this ACD response, the sensitivity analysis is in line with the pooled analyses previously presented and show a statistically significant difference in adjusted hazard ratios between degarelix and LHRH agonists for PSA PFS (overall population in CS21+CS35), CV SAEs (with or without death) in those with existing CVD, and joint-related signs and symptoms (JSS) whilst maintaining the effects of trial randomisation and minimising the impact of potential confounding variables. No hetereogeneity between studies were detected. We trust the provision of these extensive meta-analyses addresses the uncertainties of the AC committee holds and provides further corroboration of the differential efficacy and safety benefits degarelix has over LHRH agonists.*"

A fixed effects analysis assumes that the between-trial variance is zero, and weighting is therefore simply according to within-trial variance (Egger *et al* 2007). It is wise to allow for residual heterogeneity among intervention effects not modelled by the explanatory variables by conducting random effects meta-regression since the extra variability is incorporated in the same way as in a random effects meta-analysis (Higgins *et al* 2008). Trials CS35 and CS21 used different dosages of degarelix. This is regarded as a trial-level continuous covariate (Dias *et al* 2011). Since the dosing regimens were discrepant in the included trials, the between-trial variance should be included for consideration as well. The results from fixed and random effect meta-regression can be quite different therefore it is important to allow for residual heterogeneity. Otherwise the precision of estimated regression coefficients may be misleadingly overstated and sources of heterogeneity mistakenly claimed. The fixed effects analysis will not detect the clinical heterogeneity between trials CS21 and CS35 arising from the discrepant dosages of degarelix.

The manufacturer concluded that there was no suggestion of any trial heterogeneity for all outcomes analysed. This statement is stated repeatedly throughout the MR. However, this conclusion was drawn wrongly. The interaction between trial and treatment has been adjusted together with several baseline covariates. Including other covariates could explain the heterogeneity in treatment across trials. Hence, it is still uncertain if all studies included in the meta-analysis were homogeneous or not. Trial CS35 has been included despite the use of an unlicensed dose of degarelix and despite the ERG's recommendation that this trial should not be included in any pooled analyses.

Moreover it is not clear whether trials CS21 and CS35 used the same definition of PSA PFS. The MR and the clinical study report (CSR) for trial CS35 describe PSA progression /disease progression/ PSA failure as death from any cause or the introduction of additional therapy related to prostate cancer, whichever occurred first. However no such description for progression is specified in the CSR for CS21, the only definition for PSA progression/recurrence was "*2 consecutive increases in PSA levels of 50% or more and increases of more than 5 ng/ml compared with the lowest level observed*." However the Tombal *et al* (2010) paper describes that in post hoc exploratory analyses "*after the CS21 trial had completed, PCWG2 [Prostate Cancer Working Group] redefined PSA progression as a 25% increase from the baseline value along with an increase in absolute value of 2 ng/ml after 12 wk of treatment*".

5. Additional quality of life and utility mapping activities

a. Alternative mapping algorithm

Manufacturer's premise: *"We note that the ACD states the use of the Kontodimopoulos et al. (2009)10 utility mapping algorithm as inappropriate [page 36, section 4.16] and describes how the manufacturer did not provide a probabilistic estimate of the incremental cost-effectiveness ratio (ICER) [page 36, section 4.16]. Within this response, Ferring has addressed these concerns and provided utility mapping using the alternative, suggested algorithm by the AC (McKenzie and van der Pol 2009)11 and provided the requested probabilistic estimates of the ICER. These analyses, which are detailed in section 4 of this response, indicate the ICER from the updated model, which has the suggestions from the AC and ERG incorporated, is still below the recognised threshold for a cost-effective treatment."*

The new analysis was updated to use the McKenzie & van der Pol (2009) algorithm as mentioned in the ACD. This update results in slightly lower incremental QALYs. The ERG considers this change to be appropriate. The original MS included a scenario analysis (MS Table 59, page 202) which demonstrated that varying the source used for utilities from the Kontodimopoulous *et* al (2009) algorithm to the McKenzie (2009) algorithm results in a small decrease in the ICER value.

6. Additional modelling conducted

a. Revised model

The MR includes an updated cost-effectiveness model which incorporates the following changes:

i. '*Incorporation of sensitivity analysis by one-step fixed effects meta-regression model for safety and efficacy data*
ii. *Provision of additional scenario analyses around the data used to fit the curves for PSA progression for degarelix*
iii. *Development of the treatment sequence following anti-androgen withdrawal to account for the more clinically relevant treatment patterns described at the AC [meeting] (use of abiraterone before docetaxel and use of enzalutamide)*
iv. *Change in comparator drug cost to a weighted average of three-monthly LHRH agonists used in the UK, based on sales figures.*
v. *Continuation of first-line hormonal therapy until death (in line with the ERG base case presented)*

vi. *Quality of life (utility) estimates derived from the algorithm published by McKenzie and van der Pol, as recommended by the ERG.'*

Results are presented for both an updated base case and a conservative base case.

b. Incorporation of results of meta-regressions

The MR uses adjusted HRs based on a meta-regression model without a study-treatment interaction term to model PSA progression. In the MR base case the HR is applied to a parametric curved fitted to pooled data from the CS21 and CS35 trials.

The MR includes the HR from the meta-regression of 6 trials for JSS, fractures and CV adverse events. The HR is applied to parametric curves fitted to pooled data from 6 degarelix RCTs. This approach is used in a sensitivity analysis but not in the MR base case. Limitations of the meta-regressions undertaken have been discussed within the Section 2 (b) and 4 of this critique.

c. Updated parametric curve fits for PSA progression

The MS uses a lognormal curve fitted to 5 year data from the CS21 trial. The MR fits several different parametric curves to the data and found that the lognormal curves were associated with the best fit in terms of AIC and BIC.

The parametric curves were fitted to two different data sets (1) CS21 trial data, and (2) CS21 and CS35 trial data. The manufacturer chose to use the curve fit to CS21 and CS35 trial data in the base case but does not provide any explanation for this choice.

The parametric curves were fitted to both 1 year and 5 year data. The manufacturer chose to use the curve fitted to the 5 year data in the base case but does not provide any explanation for this choice. Fitting to 1 year rather than 5 year data resulted in comparatively lower survival for both degarelix and LHRH agonists and a decrease in incremental QALYs.

The MR conservative base case assumes equal efficacy after 1 year as was used in the ERG base case analysis. However, under the assumption that differential efficacy between degarelix and LHRH agonists lasts for 1 year only, the ERG consider that it would be most appropriate to fit to 1 year data, as this will produce the best fit for the time period relevant for the model.

The MR results in lower incremental QALYs presented in the MS original analysis. The ERG would suggest that it is more conventional to fit a parametric curve to the control/comparator arm and then apply the HR to this, or to model each arm assuming independent hazards.

The choice of fitting to data from both trials CS21 and CS35 results in a higher ICER (MR conservative base case £19,525) than when just CS21 trial data is used (MR conservative base case £16,004). The choice of fitting 5 year data results in lower ICER values (MR conservative base case £13,880) than when 1year data is used (MR conservative base case £16,004).

d. Introduction of enzalutamide into treatment algorithm

Manufacturer's premise: "*Enzalutamide is recommended as an option for treating hormone-relapsed metastatic prostate cancer in adults, only if: their disease has progressed during or after docetaxel-containing chemotherapy and they have not had treatment with*

abiraterone ***and*** *the manufacturer provides enzalutamide with the discount agreed in the patient access scheme*."

The MR includes treatment with enzalutamide following abiraterone and docetaxel for 24% of the population and uses the list price for enzalutamide. The MR states that the inclusion of enzalutamide is considered as a scenario analysis however it is in fact included within the MR base case (MR Appendix A: Table 13).

Enzalutamide is currently being used within the NHS. However, enzalutamide is still being considered by NICE and a FAD or PAS have not yet been agreed. The ACD 2 (released Jan 2014, guidance.nice.org.uk/TAG/354/ACD2) provides details of the anticipated use of enzalutamide:

The use of enzalutamide in sequence after abiraterone, and at list price (rather than discounted according to the patient access scheme), differs to the anticipated use suggested by ACD2. Hence, the ERG considers this change to be potentially inappropriate as it is not consistent with the anticipated use suggested by the ACD2.

7. ERG additional comments on the revised model presented in the MR

a. Update of comparator cost

The MR uses a weighted average cost (£79.64 1st cycle cost) of three monthly goserelin, leuprorelin and triptorelin for the comparator cost based on sales figures.

The ERG suggest that although 3-monthly goserelin, leuprorelin and triptorelin are all used in practice in the NHS, the use of a blended comparator is not appropriate and each of the LHRH agonists should be considered separately. Note that the least expensive 3-monthly LHRH agonist available is triptorelin (£72.07 1st cycle cost). Using 3-monthly triptorelin as the comparator results in a considerably higher ICER than using the blended comparator.

b. Mortality

The MR describes evidence for differential mortality between degarelix and LHRH agonists.

The MR includes meta-regression analyses of the 6 RCTs of degarelix versus LHRH agonists. The MR reports that among men with pre-existing CVD, the risk of CV SAEs (including death) within one year of initiating therapy was significantly lower for men treated with a degarelix compared with LHRH agonists. An adjusted HR of [redacted] is presented and the model applies the 'final adjusted' HR of [redacted]. The HR from the meta-regression is applied in a sensitivity analysis but not in the MR base cases. Limitations of the meta-regressions undertaken have been discussed within the Section2 (b) and 4 of this critique.

The MR also describes evidence for lower risk of death with slower PSA progression in metastatic patients. The MR economic model applies an increase mortality risk for metastatic progressed patients based on Hussain *et al* (2009) for the 'anti-androgen addition' and 'anti-androgen withdrawal' health states. The MR does not differ to the MS in the approach taken to model mortality.

c. Fracture risk

The MR includes a scenario analysis with a new approach to modelling the rate of fractures which does not assume proportional hazards and assumes that the rate of fractures is the same for degarelix and the LHRH agonists after 2 years. The details of the analysis are not provided within the MR. However, examination of the revised MR model provides information on the methods used. For degarelix the fracture rate for the first year is based on a fitted Weibull curve, then for the second year a linear model was assumed which is constrained such that the proportion of patients remaining fracture free for degarelix and LHRH agonists is the same after 2 years. This results in the same probability of being fracture free after 2 years between the groups, but a higher probability of fractures with LHRH agonists after 0-2 years.

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. The ERG notes that it is not possible to conclude whether the approach taken in the MR results in an improved fit to the data. A comparison of the parametric model and the Kaplan-Meier plots are not presented and Figure 29 in the MS does not include y-axis labels. Clinical input regarding the plausibility of the hypothesis regarding pathological and osteoporotic fracture rates suggested in the MR is required. Due to these uncertainties in this new modelling approach the ERG recommends a conservative analysis in which the rate of fractures is assumed to be equal for both the degarelix and LHRH agonist groups.

In the MR conservative base case fractures were excluded from the model, rather than assumed equal. The ERG notes that assuming the same fracture rate for degarelix as for LHRH agonists rather than excluding fractures entirely results in a higher ICER.

d. Additional curve fits for adverse events

Additional parametric curves were fitted to CV, JSS and fractures adverse events. For JSS and fractures the Weibull curves produced the best fit (based on AIC) so the model was not changed. For CV events the exponential curves produced the best fit (based on BIC) so the model was not changed.

In the MR base case CV, JSS and fractures adverse events were modelled using parametric curves fitted to pooled data from 6 trials included within the safety analysis. A scenario analysis was undertaken in which a parametric curve was fitted to pooled data from 6 trials in the safety analysis for degarelix adverse event rates and LHRH agonist adverse event rates are estimated via the HRs obtained from the meta-regression.

The ERG notes that although the MR has identified the curve with the best relative fit (in terms of AIC/BIC), the absolute fit remains poor and visual inspection of the curves indicates poor internal validity.

e. Updated base case definition

The updated base-case analysis includes the following changes:

- A weighted average of the costs of the 3-monthly LHRH agonists based on UK sales, and used this as the comparator
- Inclusion of HR from the meta-regression including data from CS21 and CS35 trials. The HR is applied to parametric curves fitted to pooled data from CS21 and CS35 trials degarelix arm.
- Assumes that treatment with degarelix and LHRH agonists is continued until death

- Applies utility values obtained via use of the McKenzie *et al* (2009)mapping algorithm
- An updated treatment pathway which incorporates enzalutamide and the possibility that abiraterone would be received before chemotherapy

The 'conservative base-case' includes all the changes listed above plus:

- An assumption that the efficacy of degarelix and LHRH agonists is equal after 1 year
- The exclusion of fractures

A sensitivity analysis applies the HR from the meta-regression of 6 trials for JSS, fractures and CV adverse events. The HR is applied to the parametric curves fitted to pooled data from the 6 degarelix RCTs.

f. Updated base case results

The MR presents results using the updated base case and conservative base case, see Table 1 below. In addition to deterministic results the mean results from the PSA are presented and PSA scatterplots are included within Appendix A. However, confidence intervals from the PSA results were not provided.

The MR presents results for the ITT population; a subgroup with PSA>20ng/ml; and a second subgroup with locally advanced or metastatic disease. Results for the subgroup with pre-existing cardiovascular disease were not presented. The ERG views on the appropriateness of these subgroups are discussed in Section 3 of this critique.

Table 1: ICER values for degarelix compared to weighted average of LHRH agonists

	Updated base case		Conservative Base case	
	Deterministic	PSA*	Deterministic	PSA*
Overall population (FAS)	£19,510	£14,448	£2,733	£98
PSA >20 Population	£17,516	£12,921	£4,509	£2,175
Locally advanced and metastatic population	£20,847	£14,746	£6,539	£3,325

PSA*- Probabilistic sensitivity analysis

The MR reports the ICERs for the conservative base case (with equal efficacy after one year): ITT £19,510 (PSA* mean £14,448), PSA>20ng/ml £17,516 (PSA* mean £12,920) and locally advanced and metastatic population £20,847 (PSA* mean £14,746).

The MR also presents a range of scenario analyses. Key scenario analyses are presented here:

- The MR conservative base case analysis with triptorelin (decapeptyl 3 monthly) as the comparator results in an increase in the ICER from £19,510 to £23,543.
- The MR conservative base case analysis with degarelix and LHRH agonists assumed equal in terms of efficacy results in an increase in the ICER from £19,510 to £32,065.
- The MR base case analysis with fractures risk modelled with increased hazards for degarelix to give equal risk at 2 years results in an increase in the ICER from £2,733 to £6,227.

- Scenario analyses in which the parametric curve chosen for treatment efficacy was varied demonstrated a significant impact on the resulting ICER with a range from £12,399 to £21,918 for the MR conservative base case.

g. Errors in the revised model

The new economic model included within the MR has not been fully verified by the ERG due to time limitations. However, the following inconsistencies have been identified:

- When the model is run with equal treatment efficacy and equal risk of CV events for both degarelix and LHRH agonists this results in different QALY gains for degarelix and LHRH agonists. This suggests an error in this version of the model (the formulae for the transition probability to CV death and other death use different rows for degarelix and LHRH agonists).
- The "Include_arb" parameter does not appear to be linked to the treatment pathway options and sequences on the control worksheet.

8. Conclusions

The ERG considers the claims that degarelix may offer superior benefit to comparators for patients with high risk of PSA progression and/or pre-existing cardiovascular disease were not based on robust analyses. Several inferences made in the MR were not corroborated by direct evidence. Meta-regression analyses were not conducted appropriately and the results from these updated analyses should therefore be interpreted with caution.

The additional modelling conducted within the MR incorporated several changes. The ERG considers the use of an alternative utilities algorithm; the continuation of first-line hormonal therapy until death; and the provision of additional scenario analyses to be appropriate. However, some of the updates are insufficiently justified and/or do not improve the analysis. The results from the meta-regression used within the model are associated with serious limitations as highlighted in this critique. The use of the drug cost of a blended comparator is not considered to be appropriate. The inclusion of enzalutamide is not consistent with the current NICE ACD2 for enzalutamide. Results for the subgroup with pre-existing CVD are not presented and confidence intervals around PSA* results are not provided. The MR revised model includes some inconsistencies and errors. The MR aims to address issues brought up at the AC meeting however the ERG do not believe that the MR achieves this properly. In conclusion, the ERG suggests that the results presented in the ACD from the original model provided with the MS are the most appropriate for consideration.

The ERG note that consideration of a scenario analysis which excludes SCC AEs may be important as this may represent the complement to the subgroup "patients with impending or actual spinal cord compression" (the complement of a subgroup is the overall population with the subgroup excluded). An analysis excluding SCC adverse events results in a significantly higher ICER as shown in Table 44 of the ERG report.

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