National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Degarelix for treating advanced hormone-dependent prostate cancer

You are asked to check the ERG report from School of Health and Related Research (ScHARR) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **Friday 8 November 2013** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Clarification of dosing regimen

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page number 2, the ERG report states "whilst two trials used unlicensed 3- or 6-monthly dose schedules…" That statement is incorrect – none of the six RCTs identified evaluated a 6-monthly dose of degarelix.	It is requested the wording is amended to reflect that four trials (CS21, CS28, CS30 and CS31) used the licensed dose (240 mg on initiation, followed by 80 mg monthly maintenance doses), one trial (CS35) evaluated a three monthly regimen (240 mg on initiation, followed by three-monthly doses of 480 mg at three-monthly intervals) and one trial (CS37) evaluated the licensed dose (240 mg on initiation, followed by 80 mg monthly maintenance doses) in an intermittent (6 months on, 6 months off) and continuous (12 months on) treatment setting.	The error needs correcting, since currently the design of the RCTs are being described incorrectly. There will be no impact on analyses.	Agreed. Page 2 has been amended to "whilst two trials used unlicensed dose schedules of degarelix (3-monthly or intermittent)" in the addendum.

Issue 2 Clarification of methods used for data pooling

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On pages 3, 7, 41, 80, 100, 119 and 123, the ERG discredits the use of pooled data, e.g.: 'Simple pooling ignores the characteristics of individual studies and relies on the assumption that there is no difference between individual studies' It is considered this statement is incorrect since the methods used to analyse the pooled data described	It is requested the wording in this sentence is altered to reflect that the pooled data presented within the manufacturer's submission does take into consideration the differences in trial data; since the manufacturer has access to individual patient-level data, we are able to adjust for potential	The current statement undervalues the pooled data and associated statistical methods used within the manufacturer's submission.	Not a matter of factual inaccuracy. Methods for pooled analyses were not provided. But more importantly the ERG considers that access to individual

within the manufacturer's submission does not 'ignore' the characteristics of individual studies. To confirm, all adverse events outcomes were tested for dose-dependency, i.e. to take into account difference between individual studies. This has been described previously to the ERG within the manufacturer's submission. In terms of the CV related outcome (risk of cardiovascular morbidity, with and without death) Cox proportional hazards sensitivity analysis were completed investigating the possible heterogeneity between studies, which were described within the Albertsen *et al* 2013 publication (ref. 73 within the submission). As these analyses demonstrate there was no significant sign of heterogeneity, it was not necessary to adjust for these when fitting the parametric curves.	confounding factors.		patient level data and the ability to adjust is not a substitute for meta-analysis.

Issue 3 Clarification of CS35 trial design

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page number 2, the ERG states '…a trial that using an unlicensed intermittent dose of degarelix (CS35)….' In this sentence the dose used in CS35 is described as intermittent. This is incorrect.	It is requested the work 'intermittent' is removed from this sentence.	The error needs correcting, since currently CS35 is being described incorrectly. There will be no impact on analyses.	Agreed. Page 2 has been amended to "with a trial that used an unlicensed dose of degarelix (CS35)" in the addendum.

To confirm, a continuous therapy of degarelix was used whereby a 480 mg dose was given every three months (after 240 mg on initiation).			

Issue 4 Clarification of CS35 trial design

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 32, the ERG states that 'The ERG requested justification from the manufacturer for the inclusion of trial CS35…. []…. which has an intermittent dose of degarelix versus an intermittent dose of goserelin'. In this sentence the dose used in CS35 is described as intermittent. This is incorrect. To confirm, a continuous therapy of degarelix was used whereby a 480 mg dose was given every three months (after 240 mg on initiation). Similarly, a continuous therapy of goserelin was used whereby a 10.8 mg dose was given every three months (after 3.6 mg on	It is requested the word 'intermittent' used to describe the doses of degarelix and goserelin are removed.	The error needs correcting, since currently CS35 is being described incorrectly. There will be no impact on analyses.	Agreed. Page 32 amended to "which uses a 3-monthly dosing regimen of degarelix versus a 3-monthly dosing regimen of goserelin" in the addendum.

initiation).			

Issue 5 Clarification of CS35 trial design

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 50, the ERG states '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….' In this sentence the dose used in CS35 is described as intermittent. This is factually incorrect. To confirm, a continuous therapy of degarelix was used whereby a 480 mg dose was given every three months (after 240 mg on initiation).	It is requested the word 'intermittent' used to describe the doses of degarelix and goserelin are removed.	The error needs correcting, since currently CS35 is being described incorrectly. There will be no impact on analyses.	Agreed. Page 52 amended to "trial CS35 uses an unlicensed (240mg/ 3-monthly 480mg) dose" in the addendum.

Issue 6 Clarification of CS35 trial design

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 80, the ERG states 'The manufacturer excluded trials CS35 and CS37 for some analyses on the basis of the unlicensed, intermittent dosing regimen' In this sentence the dose used in CS35 is described as intermittent. This is incorrect. To confirm, a continuous therapy of degarelix was used whereby a 480 mg dose was given every three months (after 240 mg on initiation).	It is requested the wording in this sentence is amended to reflect that CS35 did not use an intermittent dose of degarelix, i.e. used a continuous three-monthly dose	The error needs correcting, since currently CS35 is being described incorrectly. There will be no impact on analyses.	Agreed. Page 80 has been amended to "The manufacturer excluded trials CS35 and CS37 for some analyses on the basis of the unlicensed dosing regimen" in the addendum.

Issue 7 Meta-analysis rationale

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 3 and 58, the ERG states: 'Statistically significant heterogeneity was reported for the PSA response meta-analysis and no formal meta-regression was performed to	It is requested that an addition is made to the sentence that refers to the fact it is recognised as normal practice not to perform meta-regression when less than ten trials of been combined within a meta-analysis.	The current sentence suggests that the lack of meta-regression performed by the manufacturer was an oversight. The change requested would not impact on analyses but would ensure the reasoning behind why no meta-	Not a matter of factual inaccuracy. No consideration was given by the manufacturer to meta-regression or indeed alternatives to meta-regression in circumstances

justify this.' Although this statement is correct, there is no mention that meta-regression is not typically applied when meta-analyses include less than ten trials according to guidelines from the Cochrane handbook: "Meta-regression should generally not be considered when there are fewer than ten studies in a meta-analysis". (Cochrane Handbook for Systematic Reviews of Interventions. Editors Higgins & Green. Wiley-Blackwell 2008).		regression was performed is made clear to the reader.	when there are less than 10 trials for example using Bayesian techniques such as presenting the predictive distribution of studies.

Issue 8 Clarification of the equal efficacy assumption amongst LHRH agonists

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 6,7, the ERG states: 'The ERG believes that it is inappropriate to assume equal efficacy for each of the LHRH agonists.' The manufacturer considers	It is requested that the ERG amends wording to describe the manufacturer's interpretation of the clinical evidence provided (Seidenfeld *et al* 2000 and Heyns *et al* 2003) in relation to the equal efficacy amongst LHRH agonists, is in line with other interpretations of this evidence.	The current sentence is considered not appropriate when taking the available evidence into consideration.	Not a matter of factual inaccuracy. The evidence presented by the manufacturer was not sufficient to demonstrate equal efficacy of the comparators. The manufacturer is again quoting the Seidenfield

the ERG's use of the word 'inappropriate' to describe the assumption of equal efficacy amongst the LHRH agonists to be subjective. The European Association of Urology Guidelines, conclude from the Seidenfeld *et al* 2000 systematic review, which was cited within the manufacturer's submission (ref 120), that 'although only based on indirect comparison, the LHRH agonists seemed equally effective whatever their formulation'. Therefore, the manufacturer's use and interpretation of the evidence presented within Seidenfeld *et al* 2000 is in line with well-recognised, European clinical opinion. Furthermore, the results from the Heyns *et al* 2003 publication, also cited within the manufacturer's submission, indicate that for the primary endpoint (testosterone) treatment arms (triptorelin versus leuprorelin) were equivalent at 57 days, and the mean and cumulative castration maintenance rates			reference which does not include triptorelin and only uses the overall survival outcome. The manufacturer refers to the Heyns study which also includes only two of the comparators from the decision problem (triptorelin and leuprorelin) and chooses one time point (57 days) where treatment arms were not significantly different whilst a significant difference was found at 29 days. These data are not sufficient to make the conclusion that all LHRH have equal efficacy and the ERG's use of the word "inappropriate" is used to describe its interpretation of the evidence.

between days 29 and 253 were also equivalent between treatment arms, thus, providing evidence to support equivalence between triptorelin and leuprorelin.			

Issue 9 Clinical Pathway Validation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 6, the ERG states: '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 use of the word 'inappropriate' to describe the model is unjustified. The model structure presented within the submission captures how a majority of patients move through the prostate cancer pathway, as validated by the information held within the NICE CG58 guidelines, as well	It is requested the sentence is amended to reflect that the treatment sequence presented within the submission may not fully capture how all patients move through the treatment pathway, based on clinical advice received by the ERG that indicates there is variation in the treatment sequence between patients, however, the clinical advice received by the manufacturer suggests the treatment sequence presented captures how a majority of patients move through the treatment sequence.	The sentence needs correcting since, at present, the ERG considers the advice gained from the ERG clinical advisors as a higher level of evidence, when compared to the clinical advice gained by the manufacturer, but the ERG offers no justification for this assumption. The impact of this amendment will remove the bias placed upon the evidence received from the ERG clinical advisors.	Not a matter of factual inaccuracy. The ERG's statement relates to the critique of the model structure, not the clinical pathway validation.

as by the clinical experts consulted with by the manufacturer.			

Issue 10 Contradiction in the ERG's description of evidence weaknesses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 7, the ERG states: 'The study duration of the included trials was too short to make meaningful conclusions about overall survival.' Followed by: '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.' These two statements are contradictory; the first states that no great conclusions can be drawn from overall survival data, due to the short study duration (< 14 months), whilst the second statement criticises the lack of exploration	It is requested the ERG amends these statements as they are currently contradictory, therefore not fully valid.	It is requested the ERG amends these statements as they are currently contradictory, therefore not valid. The change will ensure the 'weaknesses and areas of uncertainty' described by the ERG are not contradictory.	Not a matter of factual inaccuracy. Whilst it is true that 14 months is too short to make conclusions about overall survival, the limited evidence is used to draw conclusions about efficacy without exploration of the relationships drawn from this limited analysis. Both criticisms are valid.

conducted by the manufacturer with respect to the difference in overall survival data for triptorelin, despite this trial also being < 14 months in duration (9 months).			

Issue 11 Abiraterone positioning within the clinical pathway

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 12, the ERG states 'The sequencing of abiraterone after chemotherapy is inaccurate' This statement is incorrect. The manufacturer considers the sequencing of abiraterone after chemotherapy accurate when taking into consideration current NICE recommendations; the guidance for abiraterone (TA259) clearly states *abiraterone is recommended as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if their disease has progressed on or after one docetaxel-containing chemotherapy*	The manufacturer requests that our decision to place abiraterone after chemotherapy in the treatment pathway is correct according to NICE recommendations at the time of evidence submission.	At present the sentence discounts the requirement for the manufacturer to prepare a treatment pathway in line with NICE recommendations. The impact of the change will provide reasoning of why the manufacturer submitted the treatment pathway in this format.	Not a matter of factual inaccuracy. Whilst NICE guidance CG58 recommends abiraterone only after chemo, this does not fully capture clinical practice. Clinical advice to the ERG is that abiraterone is available for patients before chemotherapy through the Cancer Drugs Fund. There may be geographical variations in clinical practice for abiraterone use and it is important for this to be highlighted to the appraisal committee.

regimen. In line with the requirements stipulated by NICE when conducting a single technology appraisal, the manufacturer has presented the clinical pathway that adheres to current NICE recommendations.			

Issue 12 Enzalutamide positioning within the clinical pathway

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 12, the ERG states: 'The diagram also omits the use of the competitive blocker, enzalutamide.' It is incorrect for the ERG to claim that the absence of enzalutamide is classed as an issue that is not accurately captured within the clinical pathway presented by the manufacturer. At the time of submission, enzalutamide had not received a final appraisal decision from NICE and therefore lacks a formal NICE recommendation. In line with the requirements stipulated by	The manufacturer requests that the manufacturer's decision to omit enzalutamide from the treatment pathway is correct according to NICE recommendations at the time of evidence submission.	At present the sentence discounts the requirement for the manufacturer to prepare a treatment pathway in line with NICE recommendations. The impact of the change will provide reasoning of why the manufacturer submitted the treatment pathway in this format.	Not a factual inaccuracy. As noted in the ERG response to issue 11, the differences in enzalutamide use in clinical practice raised by clinical advisors to the ERG to the NICE guidance need to be highlighted to the appraisal committee. Ezalutamide is now widely available (and prescribed) by clinicians post-docetaxel via the cancer drugs fund.

NICE when conducting a single technology appraisal, the manufacturer has presented the clinical pathway that adheres to current NICE recommendations.			

Issue 13 Evidence to support the relationship between androgen deprivation therapy and cardiovascular disease

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 21, the ERG states: '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' Whilst the manufacturer agrees there is a lack of prospectively designed trials to examine this relationship, the ERG omits reference to the large observational studies (that	The manufacturer requests that the ERG provides an amendment to the sentence to reflect that although there are no prospectively designed trials, there are numerous observational studies (that included a large number of patients) that have explored, and supported, this correlative relationship between androgen deprivation therapy and cardiovascular mortality.	At present, this paragraph omits the other available evidence that has explored the correlative relationship between androgen deprivation therapy and cardiovascular mortality. The amendment will provide the reader with a more detailed explanation of what evidence is available i.e. although there are no prospectively designed trials, there are numerous observational studies (that included a large number of patients) that have explored, and supported, this correlative relationship.	Not a matter of factual inaccuracy. The ERG report currently already raises the fact that there exists much correlative evidence but does not claim to provide an exhaustive list of the observational evidence. The ERG make the point that this correlative evidence has yet to be explored in prospective trials.

included up to 73,000 patients) that have examined, and supported, this correlative relationship as referenced within the manufacturer's submission: ref. 111 Keating *et al,* 2006; ref. 112 D'Amico *et al*, 2007; ref. 113 Saigal *et a*l, 2007; Keating et al, 2010 and ref. 115. Lester-Coll et al 2013.			

Issue 14 Search strategy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 22, the ERG states: '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' Although the statement is correct that 'mapping' was not used, the terms used in the search strategies across the three databases were	The manufacturer requests that the ERG amends the sentence to convey that, although mapping was not employed, the manufacturer included a comprehensive list of search terms, which were both relevant to degarelix and the LHRH agonist comparators.	At present, these sentences do not convey that the manufacturer included a comprehensive list of search terms, which were relevant to both degarelix and the LHRH agonist comparators.	Agreed. Amended page 22 to: "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

sufficiently comprehensive and relevant to both degarelix and LHRH agonist comparators, so it is extremely unlikely that any relevant published trials have been missed.			retrieval (recall and precision).” In the addendum.

Issue 15 Definition of the design/mechanism of action of LHRH agonists

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 43, the ERG states ‘LHRH agonists which are essentially designed to simulate surgical castration’ The manufacturer believes this is incorrect. Initial treatment with LHRH agonists does not simulate castration. The mechanism of action of LHRH agonists is to initially increase luteinising hormone (LH) release; it is only on prolonged administration that results in the inhibition of pituitary LH secretion. Conversely, the design of GnRH antagonists more closely mimics surgical castration; GnRH antagonists	The manufacturer requests that the ERG amends the sentence to more accurately reflect the mechanism of action of LHRH agonists.	At present, these sentence incorrectly describes the mechanism of action of LHRH agonists by discounting their initial effects on testosterone levels. The requested amendment will ensure the reader is aware of the mechanism of action of LHRH agonists.	Not a matter of factual inaccuracy. Despite the mechanism of action, the aims of the LHRH agonists and GnRH antagonists are the same: to simulate surgical castration.

cause a rapid reduction in LH and follicle-stimulating hormone (FSH) without the initial increase in levels as seen with LHRH agonists. Surgical castration does not induce the transient increase in LH that is seen with LHRH agonists, therefore this statement is incorrect.			

Issue 16 Conclusions drawn from meta-analysis data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 59, the ERG states 'This large heterogeneity could indicate that the two different comparators (leuprorelin and goserelin) are quite different' The manufacturer suggests it is incorrect for the ERG to provide only one reason for the heterogeneity described, without any evidence to back up this statement.	The manufacturer requests that the ERG removes this explanation, provides evidence to support this sentence or describes all possible reasons for the heterogeneity.	At present, this sentence is speculative and not based on supportive evidence.	Not a matter of factual inaccuracy. It is not the ERG's responsibility to explain heterogeneity but it is the responsibility of the ERG to highlight where it is evident and what may be the cause.

Issue 17 Justification provided to support the assumption of equal efficacy amongst LHRH agonists

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 58 and 60, the ERG states 'No justification has been given for assuming leuprorelin and goserelin have equivalent efficacy.' The terminology of 'no justification' is incorrect. As detailed within the manufacturer's submission the following justification was provided: The mixed treatment comparison showed no statistically significant differences in the overall survival outcome between the different LHRH agonists, thus supports previous reports by ref. 120 Seidenfeld *et al* 2000 and ref. 121 Hemels *et al* 2002 that none of the LHRH agonists exhibit superior clinical efficacy or effectiveness over another. A justification was provided by the manufacturer, however it would appear that the ERG does not agree with this justification.	The manufacturer requests that the ERG amends the wording to reflect that a justification was provided by the manufacturer.	At present, this sentence suggests that no evidence was presented by the manufacturer to support the equivalent efficacy assumption between the LHRH agonists, which is incorrect.	Agreed. Pages 58 and 60 have been amended to: "sufficient justification has not been given for assuming leuprorelin and goserelin have equivalent efficacy" in the addendum.

Issue 18 Clarification of search strategy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 61, the ERG states '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.' This is incorrect. As described in the manufacturer's submission, the search filters applied to account for study design were '#13: #12 Filters: Clinical Trial; Meta-analysis; Systematic Reviews', which would identify both RCTs and non-RCTs. Therefore non-RCT evidence was identified and searched in a systematic way.	The manufacturer requests the wording is amended to reflect the both RCT and non-RCT trials were identified using the search terms applied by the manufacturer in a systematic way.	The ERG has incorrectly suggested the search strategy employed would not have identified non-RCT evidence in a systematic way.	Not a factual inaccuracy. The manufacturer has selected a quote which omits the next sentence on page 61 which critiques the retrieval of non-RCT evidence "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."

Issue 19 Reference numbering

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 96 the same reference is being used for two separate reference numbers. 'A study by Scher *et al.,* (2013)[45] suggests PSA progression is inappropriate as a surrogate endpoint[29,45] 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. 45. 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. The study should only be	Delete duplication of reference.	Shows to the reader that only one reference is available to support the referenced finding.	Agreed. Page 96 has been amended to delete this duplicate reference (no. 45) and an updated bibliography has been included in the addendum.

referenced by one number. This suggests there are two separate publications suggesting PSA is an inappropriate endpoint.			

Issue 20 Clarification of CS37 trials design

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 60 the ERG states: 'whilst trial CS37 which also used an unlicensed dose of degarelix is excluded' This is incorrect, the dose used in CS37 is the licensed (240 mg / 80 mg) dose. It is in fact that the intermittent use of degarelix was employed within CS37, which is not used in practice and is unlicensed, was the reason for exclusion of CS37 from the meta-analyses.	Amend statement to show CS37 was excluded on the basis it used an intermittent dosing regimen, opposed to an unlicensed dose.	Currently, the design of CS37 is being described incorrectly.	Agreed. Page 60 has been amended to: "whilst trial CS37 which also used an unlicensed intermittent dosing regimen of degarelix is excluded" in the addendum.

Issue 21 The use of Scher *et al* 2013 paper

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 96, the ERG states: '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 manufacturer suggests the use of the Scher *et al* 2013 paper to discredit the use of PSA progression in the model submitted by the manufacturer is incorrect. The Scher *et al* 2013 discredits the use of PSA progression as a biomarker for overall survival, but only in	The Scher et al 2013 paper is removed, and not used as evidence by the ERG to discredit the use of PSA progression in the HE model submitted by the manufacturer.	The use of the Scher *et al* 2013 paper to discredit the use of PSA progression as a surrogate marker for disease progression/overall survival in hormone-dependent prostate cancer patients is not valid and discredits the model submitted by the manufacturer unfairly.	Partial agreement. The Scher paper has not been removed however page 96 has been amended to: "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]" in the addendum.

castration resistant prostate cancer patients (CPRC).To clarify, the manufacturer did not use or apply differential efficacy in PSA progression (as a surrogate marker for disease progression) in castration-resistant prostate cancer patients within the model submitted.			

Issue 22 Clarification of the dates for the Scottish registry

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 90: "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."	"The approach to survival modelling applied a different mortality rate for patients receiving abiraterone. The ERG believes that this is likely to be appropriate as the Scottish registry data population which informs relative survival did not include patients who received abiraterone. Abiraterone only received a European licence in September 2011 and the registry data used only includes patients up to 2007."	Given the dates of the registry data (up to 2007) use of abiraterone would not have been included (the Phase III trial started in 2008).	Not a matter of factual inaccuracy. The original MS did not give details of dates of Scottish registry data so the ERG report was based on the information provided at the time.

The dates of the registry data used do not coincide with either European marketing authorisation of the Phase III trial therefore inclusion of abiraterone treatment effect within the registry data is highly unlikely.			

Issue 23 ERG statement regarding analysis of mortality

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 96: "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." This is easily done within the current model structure by replacing the non-metastatic and metastatic prostate cancer survival columns (J and N in the mortality sheet) with the total prostate cancer survival (column I).	Present analysis in which degarelix impacts on PSA progression and not overall survival using total prostate cancer survival. This results in a dominant ICER using the base case model supplied as part of ERG questions (incremental costs £1,684 and incremental QALYs 0.56) and an ICER of £14,916 using the ERG base case as detailed on page 114 (incremental costs £3,577 and incremental QALYs 0.24)	It is possible to easily present the analysis requested by the ERG.	Not a matter of factual inaccuracy. Whilst the analysis provided by the manufacturer is useful and welcome, it does not represent an omission of fact by the ERG. It would be a dangerous precedent to amend submitted reports based on new data. For this reason we have not changed the report.

Issue 24 Clarification regarding probabilistic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 122: “The model used to undertake the PSA was not provided by the manufacturer and so this could not be checked by the ERG.” The model used for probabilistic analysis was provided.	Remove this sentence or clarify to say lognormal distributions or updated distributions	This statement is incorrect as the model used to undertake PSA (using original distributions) was provided. The model used to undertake PSA for lognormal distributions is additionally provided with this clarification.	Agreed but appears on page 113 (not page 122). Page 113 has been amended to: “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.” in the addendum.

Issue 25 Statement that sensitivity analyses were not supplied

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 118: “The MS presents the following result of the sensitivity analyses. These results were produced using the uncorrected model and were not updated when the	Remove the last sentence	This statement is incorrect as updated results were provided in the response to the initial ERG clarification in Appendix 9 (Appendix 10 for the model continuing treatment until death)	Agreed but appears on page 109 (not page 118). Page 109 has been amended to: "These results were

model was corrected. These results were produced using the uncorrected model and were not updated when the model was corrected." Sensitivity analysis results were supplied.		for all sensitivity analyses.	produced using the corrected model included within the manufacturer's response to clarifications**."** in the addendum. Appendix 9 Table 8 has also been included in the addendum to replace the current Table 41: Deterministic model results for sensitivity analyses on parameter values (pages 110-112 of the addendum)

Issue 26 Clarification of costs of SCC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 105: "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	None – further detail provided for clarification to the ERG	The correct values (as used within the model) are presented in Table 32 which as identified by the ERG are weekly costs. These do originate from Table 42 (original source is the publication by Lu et al) as identified by the ERG. The values reported in Tables	Noted.

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." Clarification is provided for the ERG to the right.		48 and 51 should be ignored.	

Issue 27 Clarification of the dates for the Scottish registry

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg100: "The data presented in Figure 29 of the MS has no events after around 112 days for the degarelix	"The Kaplan Meier data presented in Figure 29 of the MS has no events after around 112 days for the	For clarity as this is not the assumption in the model where events are still assumed to	Not a factual inaccuracy. The current sentence does not misconstrue the type of

arm." Missing words Kaplan Meier.	degarelix arm."	occur beyond this point.	analysis as something other than Kaplan Meier.

Issue 28 Definition of PSA response

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 20 and 43: There has been a misunderstanding over the definitions for 'PSA response' and 'PSA progression'. To confirm: In table 11 on page 43, 'PSA response' includes trials that have reported the PSA outcome using: A) Absolute changes in PSA from baselines, and/or B) PSA progression data, which is defined as 'two consecutive increases of 50% or more above the PSA nadir (the lowest level observed)'	No amendments required.	No amendments required.	Noted

Please note that, only PSA progression data from CS21 has been implemented within the HE model presented within the submission.			

Issue 29 Clarification of methods used for data pooling

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 42, the ERG states: 'In addition to the flawed method of simple pooling, there were significant differences in the baseline characteristics of these two groups' when referring to the pooling of CS21 and CS35 data. Although there are differences in the baseline characteristics of patients within the CS21 and CS35 trials the pooled analysis presented by the manufacturer adjusted for these factors. To confirm, within the pooled analysis of CS21 and CS35: PSA PFS failure rate was	The addition of a statement to indicate that adjustments were made for patient characteristics to address any imbalances that may be presented between the CS21 and CS35 trial populations.	Currently the description of the pooled analysis discounts any of the adjustments the manufacturer made.	Not a matter of factual accuracy. Whether or not adjustments were made, the baseline characteristics were significantly different.

adjusted for baseline PSA, PCa stage and Gleason score and the overall mortality rate was adjusted for age, baseline PSA, PCa stage and Gleason score. Therefore, any imbalances should be addressed by the adjustments made.			

Issue 30 The applicability of testosterone to be used as a surrogate marker for overall survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 38, the ERG states: '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.'	The manufacturer requests the ERG either retract this last sentence, or provides evidence to support the link between testosterone and overall survival.	Currently no evidence has been provided by the ERG to describe the correlative link between testosterone response and overall survival.	Not a matter of factual inaccuracy. The ERG report does not state that testosterone response is surrogate for OS but instead states that biological criteria, can be regarded as surrogates for patient relevant criteria such as OS.

The manufacturer questions if the use of testosterone as a surrogate outcome for patient-relevant clinical endpoints, such as survival is factually correct; the ERG has not provided evidence for the link between testosterone and overall survival.			