NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Degarelix for treating advanced hormone-dependent prostate cancer [ID590]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Ferring Pharmaceuticals
   - Prostate Cancer UK
   - British Association of Urological Surgeons
   - British Uro-Oncology Group

   The Department of Health submitted a 'no comments' response and we did not receive any comments on the ACD from the clinical or patient experts.

3. **Comments on the Appraisal Consultation Document received through the NICE website**

4. **Additional evidence from** Ferring Pharmaceuticals:
   - Further information on additional evidence
   - Tabulated results incorporating discount
   - Delphi study results to validate findings of expert advisory board (appendix A)
   - SMC predicted uptake (Appendix C)
   - CMU National branded framework agreement Ferring (Appendix D)
   - NHSE Testimonial regarding current rebate (Appendix E)
   - Ferring cost effectiveness results including list price discount (Appendix F)

5. **Evidence Review Group critique of Ferring's additional evidence** from School of Health and Related Research (ScHARR)
   - Additional ERG analyses (including list price discount)
   - Addendum report (additional ERG analyses using list price discount and the DSU model)

6. **Additional analyses provided by the Evidence Review Group following the committee meeting on 4 November 2015**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Single Technology Appraisal

Degarelix for treating advanced hormone-dependent prostate cancer

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
British Association of Urological Surgeons	In the view of BAUS, the conclusion of this draft ACD for ID590 not to use Degarelix for any indication is disappointing. BAUS feels Degarelix should be approved by NICE for use in the emergency setting of spinal cord compression (bearing in mind the difficulties in identifying patients at risk of SCC, the indication may be restricted to established spinal cord compression [SCC]) and bilateral ureteric obstruction due to hormone-naïve prostate cancer. The rapid achievement of a castrate testosterone in this group of patients should make it the drug of choice and equivalent to bilateral orchidectomy. It is well-established that most advanced prostate cancer patients prefer medical treatment to bilateral orchidectomy. Standard methods of medical androgen deprivation take 4 weeks to achieve castrate testosterone, during which time disease may progress causing further irreversible clinical deterioration. Continuation of long-term androgen deprivation therapy in these patients could be using LHRH analogues unless the difference in cost between these drugs becomes insignificant; current evidence for superiority of degarelix over LHRH-analogues in terms of prolonged time to disease progression and reduction in cardiovascular disease risk is not above criticism and more robust evidence is awaited.	Comment noted. The FAD recommends degarelix as an option for treating advanced hormone-dependent prostate cancer in people with spinal metastases, only if the commissioner can achieve at least the same discounted drug cost as that available to the NHS in June 2016.

Consultee	Comment [sic]	Response
British Uro-oncology Group	On behalf of the British Uro-oncology Group (BUG), we would like to document our extreme disappointment over the ACD proposal that: '1.1 Degarelix is not recommended within its marketing authorisation for treating advanced hormone-dependent prostate cancer' and urge NICE to reconsider this position. We would propose that degarelix should be available as an option for: • men with high volume advanced (metastatic) disease who will benefit from immediate therapy with rapid reduction to testosterone and will avoid catastrophic consequences of any tumour flare eg spinal cord compression There is enthusiasm to have the opportunity to prescribe degarelix amongst oncologists and urologists who treat prostate cancer. This latest ACD decision is extremely disappointing for clinicians and patients who are suffering with advanced prostate cancer. We appreciate that the amiable data are not all Level 1 evidence and that some of the articles are looking at post hoc analyses, pooled data and subgroups. However, there are consistently strong signals from all these studies that when considered together add up to providing convincing evidence that degarelix could be a more effective drug in terms of delaying the time to a castrate resistant state and is also safer with less risk of cardiovascular events and death. For these reasons we feel that clinicians should have the choice to prescribe the most effective drug at the initial stages of the disease, particularly if this can reduce cardiovascular disease progression – the consequences for the patient and the financial implications. The evidence from the pivotal CS21 study entitled: Efficacy and Safety of Degarelix: a 12 month, comparative, randomised, open-label, parallel-group phase III study in patients with prostate cancer, Klotz L et al. BJUI 2008, demonstrated the non inferiority of degarelix in addition to immediate biochemical and clinical effectiveness without flare or the need for any additional flare protection. Degarelix was shown to achieve immediate testosterone reduction with a rapid PSA decrease and faster control of prostate cancer. The very low testosterone levels were maintained with degarelix. Degarelix was shown to be a well-tolerated alternative to LHRH agonists with a good safety profile. There have been some previous discussions over the fact that only 11% of men received an antiandrogen to prevent initial testosterone flare. The use of an antiandrogen does not totally block testosterone and the data comparing LHRH agonists to orchidectomy show some inconsistencies and it would appear that even when an antiandrogen is prescribed, this does not achieve total blockade of testosterone. The fact that whether an antiandrogen was administered or not with the initial injection does not prevent the ongoing testosterone miniflares and surges with subsequent injections. It is very possible that the immediate and continued superior suppression of testosterone accounts for the increased efficacy of degarelix seen in the post hoc analyses. The data from further analyses show consistent signals to suggest that degarelix is a potentially more effective choice especially for men with high risk advanced (metastatic) prostate cancer. 1. Degarelix also demonstrates a more rapid and sustained suppression of FSH than LHRH agonists (CS21) and a further study of FSH was demonstrated in the 160616 [sic] study when men treated with leuprorelin were changed to degarelix (CS21A). FSH is thought to have an impact on prostate cancer progression and has been	Comment noted. The FAD recommends degarelix as an option for treating advanced hormone-dependent prostate cancer in people with spinal metastases, only if the commissioner can achieve at least the same discounted drug cost as that available to the NHS in June 2016.

Consultee	Comment [sic]	Response
Prostate Cancer UK	1.Has all of the relevant evidence been taken into account? No. One of the key contributing factors to NICE's draft decision not to recommend degarelix within its marketing authorisation for treating advanced hormone-dependent prostate cancer was an inability to define and quantify the patient subgroup for which degarelix would be the optimal treatment. Clinical experts advised the Appraisal Committee that degarelix is particularly appropriate for men at high risk of disease progression. This patient subgroup was defined as those with a prostate specific antigen (PSA) level of more that 20 ng/ml, older men, those with pre-existing cardiovascular disease, and those with spinal metastases. NICE clinical guideline 175, Prostate cancer: Diagnosis and treatment, recommends bilateral orchidectomy as an alternative to continuous luteinizing hormone-releasing hormone (LHRH) agonist therapy (1). The Appraisal Committee does not appear to have considered quantifying the subgroup of patients using Hospital Episode Statistics (HES) data on bilateral orchidectomy. Bilateral orchidectomy rates may be an indicator of treatment for those men who are unsuitable for treatment with LHRH agonists and therefore use of this data could be used to quantify the subgroup for which degarelix would be a valuable treatment option. In addition, the Appraisal Committee does not appear to have considered analysing rates of diagnosis for high-burden disease. This could be achieved by analysing PSA levels at diagnosis, although it would not provide information on men who go on to develop advanced prostate cancer.	Please see section 4.14 of the FAD. The FAD recommends degarelix as an option for treating advanced hormone-dependent prostate cancer in people with spinal metastases, only if the commissioner can achieve at least the same discounted drug cost as that available to the NHS in June 2016.
Prostate Cancer UK	2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No. According to the British National Formulary (BNF), a starting dose of degarelix (Firmagon®) (240mg administered as two 120mg/3mL subcutaneous injections) costs £260 at list price. Subsequent maintenance doses (80mg/4mL administered as one subcutaneous injection every month) cost £129.37 at list price (2). At its list price, the total annual cost of degarelix is £1,683 in the first year and £1,552 thereafter. This compares to an average annual cost of £953 (range = £760-£1,324), plus a three-week anti-androgen course averaging £26 (range = £6-£55), for currently available LHRH agonists (2). At its list price, degarelix costs an average £704 more per patient in its first year and £573 more thereafter, compared with the average annual cost of treating a patient with a currently available LHRH agonist. We do not consider this to be a significant cost difference in relation to the benefit men who are unsuitable for LHRH agonists would gain from treatment with degarelix. Furthermore, NICE clinical guideline 175 recommends bilateral orchidectomy as an alternative to continuous LHRH agonist therapy (1). We understand the approximate cost of a bilateral orchidectomy is £1,000 . Although this is a lower cost treatment, the physical and emotional impact of such an operation on men should not be under-estimated. Finally, we believe that the manufacturer's proposed Patient Access Scheme (PAS) should be accepted by NICE, as it has been in Scotland (3) and Wales (4), to ensure the best value for the NHS.	Comment noted. The FAD recommends degarelix as an option for treating advanced hormone-dependent prostate cancer in people with spinal metastases, only if the commissioner can achieve at least the same discounted drug cost as that available to the NHS in June 2016.

Consultee	Comment [sic]	Response
Prostate Cancer UK	3.Are the provisional recommendations sound and a suitable basis for guidance to the NHS? No. According to NICE clinical guideline 175, the only active treatment alternative to continuous LHRH agonist therapy that can currently be offered to men with metastatic prostate cancer is bilateral orchidectomy (1). This is an undesirable alternative treatment option for many men who are unable to receive continuous LHRH agonists due to its irreversibility and the consideration of the impact of major surgery on recovery, as well as its emotional impacts. Degarelix is, therefore, an important treatment option that should be made available to appropriate men on the NHS.	Comment noted. The FAD recommends degarelix as an option for treating advanced hormone-dependent prostate cancer in people with spinal metastases, only if the commissioner can achieve at least the same discounted drug cost as that available to the NHS in June 2016.
Prostate Cancer UK	4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Yes. The proposed recommendations would be of detriment to the care of older men. Clinical experts advised the Appraisal Committee that degarelix would be particularly appropriate for older men. Older men with prostate cancer are significantly less likely to undergo surgical procedures as part of their treatment (5,6). With bilateral orchidectomy as the only alternative active treatment option for men unsuitable for LHRH agonists, treatment options are therefore severely limited for older men at this stage of the prostate cancer treatment pathway. We believe degarelix should be available for these men	Comment noted. The FAD recommends degarelix as an option for treating advanced hormone-dependent prostate cancer in people with spinal metastases, only if the commissioner can achieve at least the same discounted drug cost as that available to the NHS in June 2016.
Ferring Pharmaceuticals	Ferring appreciates this opportunity to address the recent ACD in respect of degarelix, to support our previous submission. We shall aim to demonstrate our belief, consistent with that of many expert clinicians in this field, that degarelix is a clinically effective option for the treatment of men with advanced, hormone-dependent prostate cancer in a defined subgroup and that it is cost-effective in this group. We will address three key issues arising from the draft recommendation: 1. a clinically derived and workable definition for the sub group suitable for this treatment 2. a review of cost efficacy of antagonists over agonists in the sub group – taking into account the cost benefit of rapid symptom relief on hospital stay 3. pricing policy – Ferring is looking at mechanisms to reduce the acquisition cost of degarelix further in order to enhance the cost effectiveness to the NHS in the defined populations. In providing this additional information, supporting results and clinical data, we seek a positive outcome from the Appraisal Committee that will benefit patients across England.	Comment noted. The FAD recommends degarelix as an option for treating advanced hormone-dependent prostate cancer in people with spinal metastases, only if the commissioner can achieve at least the same discounted drug cost as that available to the NHS in June 2016.
Ferring Pharmaceuticals	1. Sub group of patients suitable for treatment with degarelix. Ferring convened an expert advisory board to address the challenge of developing a clear description of the specific, in-label patient population(s) that are most suitable for treatment with degarelix. The expert advisory board comprised six Urology Consultants from a range of units in England. Using a nominal group technique, the clinicians defined the symptomatic, diagnostic and differential elements of the patient groups they considered most suitable for treatment with degarelix. They graded the level of evidence that supported their decision and	Comment noted. The FAD recommends degarelix as an option for treating advanced hormone-dependent prostate cancer in people with spinal metastases, only if the commissioner can achieve at least the same discounted drug cost as that available to the NHS in

Consultee	Comment [sic]	Response
	reached consensus on several defining characteristics. The findings of the advisory board were tested in a two-round, web-based Delphi consultation (see Appendix A for methods and results). After removal of two experts who failed to meet the screening criteria for the consultation, a total of 61 experts participated in round 1, of which 47% (n=29) also completed round 2. At the time of the consultation, all Delphi panellists had direct clinical responsibility for patients with advanced hormone-dependent prostate cancer being treated with either degarelix or a luteinising hormone-releasing hormone (LHRH) agonist. The Delphi consultation reached consensus on the following universal descriptor: **Degarelix should be considered for patients presenting with symptomatic and/or high-volume metastatic, hormone-dependent prostate cancer** – characterised by any one of the following; • **painful bony metastases** • **high-volume bony metastases (≥4; with one outside the pelvic/spine region – based on the STAMPEDE/ CHAARTED trial definition)** • **ureteric obstruction** • **systemic signs of cancer; eg, weight loss, depression, anorexia, anaemia** • **high potential for spinal cord compression** • **pre-existing cardiovascular disease** On the basis of substantial validated clinical opinion and experience, Ferring would ask the Committee to accept this patient sub group in its consideration for recommendation. In addition, consensus was reached on supporting statements for consideration in treatment, as follows: • **LHRH antagonists are less cardiotoxic than LHRH agonists** • **LHRH antagonists are less likely to cause undesirable, cardio-related consequences than LHRH agonists** • **LHRH antagonists provide a more rapid control of serum testosterone levels than LHRH agonists, and, therefore, should be considered as a treatment option to control the acute symptoms related to advanced, hormone-dependent prostate cancer** The above consensus statements support the second key issue addressed below.	June 2016.
	2. Efficacy of Antagonists over Agonists In the recent draft ACD recommendation there is an assumption that degarelix, a novel GnRH antagonist, is clinically the same as a LHRH agonist. However, we respectfully disagree with this assumption and we set out	Comment noted. Please see section 4.22 of the FAD. The FAD recommends degarelix as

Consultee	Comment [sic]	Response
	some of the key differences in the section below. We specifically wish to address the committee's interpretation of testosterone flare. The committee acknowledged that degarelix is particularly beneficial for avoiding testosterone flare, which may have led to the initial recommendation in the original ACD (pre-appeal) for use in patients at risk of spinal cord compression. Ferring appreciates the fact that the committee did attempt to find a sub-group where it could recommend degarelix. The focus on flare avoidance, however, is potentially misleading. The key benefit that degarelix offers is a rapid reduction in testosterone and other sex hormones such as FSH and LH2. This suggests optimum use of degarelix in patients who present with bone pain, bladder outlet/ureteric obstruction, lumbar back pain and hydronephrosis. By contrast, to use an agonist in this situation would result in a 7 to 10 day delay whilst an anti-androgen can take effect, leading to a possible increased risk of complications, a poorer quality of life, additional hospital bed occupancy and potential adverse consequences such as spinal cord compression and bladder outlet/ureteric obstruction. The Committee did in fact note that Ferring were not given the opportunity to present a cost-effectiveness case at the last appraisal committee meeting in patients who would benefit from a rapid reduction in testosterone (page 60 of the AC document). This cost-effectiveness case is therefore presented within this response. In accordance with the appeal decision, only benefits that are related to the group of patients at risk of spinal cord compression are included. These include: • reduction in the rate of SCC • reduction in the length of stay associated with initial inpatient admission whilst treatment takes effect • increase in quality of life (as demonstrated in the more severe subgroups in CS21). The resulting cost-effectiveness analysis demonstrates that in the subgroup of patients who would be treated with degarelix in clinical practice (i.e. those patients for whom a rapid reduction in testosterone would be beneficial) degarelix is highly cost-effective, proving to be dominant in all clinically realistic scenarios (see appendix B). Ferring maintains that there are differences in the associated cardiovascular risk for patients being treated with agonists compared to degarelix. Our feeling is that the evidence on this has been given insufficient weight, perhaps due to the fact that the evidence for agonists causing a problem was not considered in the original review, the belief that cardiovascular issues are caused by metabolic changes over the longer term due to androgen deprivation and also due to a (mis)interpretation that degarelix is cardio-protective. By considering the data that support an effect of agonist treatment on the incidence of CV events, this in turn helps to explain the relative risk reduction that has been observed with degarelix. This effect is a significantly reduced risk, particularly in the short term rather than because degarelix inherently lowers the risk, in the manner, say of a statin. Hence why the reduction in risk is observed in the first year.	an option for treating advanced hormone-dependent prostate cancer in people with spinal metastases, only if the commissioner can achieve at least the same discounted drug cost as that available to the NHS in June 2016.
	3. Pricing Policy Despite the fact that a universal rebate is offered by Ferring and is in operation across the NHS, the current health economic modelling has been conducted on the existing trade price for degarelix. Unfortunately, due to the peculiarities of the NHS transactional flow in primary care, the Department of Health was unable to approve the	Comment noted. The FAD recommends degarelix as an option for treating advanced hormone-dependent prostate cancer in

Consultee	Comment [sic]	Response
	Patient Access Scheme accepted by, and used in, Scotland and Wales. Ferring is currently pursuing options to reduce the acquisition price of degarelix and asks that the Committee acknowledge these options, and make a supportive recommendation, subject to achieving a target acquisition cost of between £221 - £234 for the initiation dose and £109.96 - £116.43 for the maintenance dose, to commence at publication of the FAD (we note a similar approach was taken in the NICE technology appraisal recommendations for drug-eluting stents). These prices have been modelled through the revised HE models and are presented for reference in appendix F. Ferring is exploring different options to achieve these target prices, which include - but are not limited to - the following: • Simple price reduction • Price reduction and free starter pack to hospitals • Discount applied to packs delivered directly by a home care company or wholesaler, either to the GP practise or patient's home • CMU tender. Additionally the discounted price offered via the existing national tender in place at the CMU and any existing CCG contracts will be honoured.	people with spinal metastases, only if the commissioner can achieve at least the same discounted drug cost as that available to the NHS in June 2016.
Ferring Pharmaceuticals	Other key differences between GnRH Antagonist and LHRH Agonists Role of s-ALP and rate of fractures There was an assumption that fractures would increase over time for both therapies, given that ADT leads to a reduction in bone mineral density. This ignores the evidence from Schroder et al3 that demonstrates that serum alkaline phosphatase, a well-established endpoint with large predictive value for several cancer forms that metastasise to the skeleton, is controlled better and for longer in degarelix compared to an agonist. Better control of cancer activity in the bone would lead to a reduction in pathological fractures. The ERG stated that the results should be interpreted with caution because "only the statistically significant finding from a post-hoc subgroup analysis of patients with metastatic disease was reported" (section 3.25) and that baseline characteristics were not presented. This is contrary to the data: • High S-ALP can only be present in patients with metastatic disease and indeed bone metastases • Baseline characteristics are presented in the paper published by Schroder et al 20103 The introduction of new therapies for late-stage prostate cancer like cytotoxic therapy, abiraterone or enzalutamide has again shown the value of S-ALP as a measure of disease volume within the skeleton and also as a prognostic marker4, 16. S-ALP has a value independent of, and superior to PSA, in many patients with advanced skeletal metastasis. Schroder et al 2010 (3) shows the better ALP suppression of degarelix compared with leuprolide and Klotz et al 2014 (2) confirms this. Patients without skeletal metastasis don't have elevated PSA and don't show an ALP response to treatment and serve as good control groups. Schroder et al 20103 showed that the superiority of degarelix is greater when there is more disease in the skeleton illustrated in the patients with low Hb (<13 g/dL). These groups also represent patients where the negatives/dangers of surge/flare are the greatest. The agonists are even contraindicated in the most advanced groups. A serious warning is issued for agonists due to surge/flare5,6,7. Patients in these groups would need to have surgical orchidectomy or have a surge during agonist treatment w/wo antiandrogens if degarelix is not available. This lack of an appropriate medical treatment	Comment noted. See section 4.16 of the FAD.

Consultee	Comment [sic]	Response
	would potentially cause considerable harm.	
Ferring Pharmaceuticals	Cardiovascular effects The lack of the effect of Degarelix on serious cardiovascular events was not given the prominence it perhaps deserves based on 3 main assumptions: • The increase in conventional cardiovascular risk factors was due to androgen deprivation (section 4.10) – changes in blood lipids, increased plasma insulin levels & increased risk of metabolic syndrome – hence there would be no difference between Degarelix and an agonist as both lower testosterone to the same level • The paper by Albertsen et al8 was a pooled analysis and hypothesis generating only • The belief that Albertsen results were driven mainly by the inclusion of one small study that showed a relative risk reduction of 80% which was felt to be implausible In addressing the points above: If the difference in CV events was purely driven by ADT then it would be reasonable to assume that an agonist would have the same effect as bilateral orchiectomy. However, several large studies have highlighted a clear difference in associated risk of CHD, MI & sudden cardiac death in patients treated with LHRH agonists compared to orchiectomy (Keating 20069, Gandaglia 201010). It would be unreasonable therefore to conclude that increased CV risk is solely down to ADT. These data were not considered fully by the committee in reaching their conclusion. Agonists increase the risk of a thromboembolic event (MI etc) in the shorter term (Gandaglia10). There is no evidence, however, to suggest that antagonists increase that risk. Indeed the FDA published the following statement in October 2010: “The U.S. Food and Drug Administration (FDA) has notified the manufacturers of the Gonadotropin-Releasing Hormone (GnRH) agonists of the need to add new safety information to the Warnings and Precautions section of the drug labels. This new information warns about increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke) in men receiving these medications for the treatment of prostate cancer.” Underlying risk is also driven by the presence of pre-existing CV disease. A plausible explanation of how antagonists avoid risk appears to have been misinterpreted by the Committee which refers to “degarelix’s potential effect of reducing inflammation linked with atherosclerosis”. Degarelix does not claimed to reduce inflammation or to be a secondary prevention therapy; it simply does not exacerbate the risk to the same extent. Albertsen8 results were presented both as the original pooled analysis and as a meta-analysis. In both analyses a statistical difference was observed between Degarelix and the agonist in terms of overall risk – favouring degarelix. By focussing solely on Albertsen8, though, the Committee is ignoring the evidence referred to above that demonstrates the negative impact that agonist therapy has on CV risk and that led to a warning being issued by the FDA11. The results of 3 key studies drive the overall result of Albertsen8 and all favour degarelix. The 80% relative risk reduction observed in one of these may have been misinterpreted by the committee. If Degarelix was considered to be cardioprotective then the 80% RRR would seem incredible given that statins only reduce relative risk by up to 40%12. However, Degarelix is not cardioprotective and should not be interpreted as such. The apparent relative risk reduction is driven by the level to which the agonist increases risk and it is the significantly lower risk	Comment noted. See section 4.16 of the FAD.

Consultee	Comment [sic]	Response
	of degarelix that drives the relative reduction.	
Ferring Pharmaceuticals	***Health Economic Assessment*** **Context** Overall the Committee concluded that the ICERs presented by the ERG based upon ITT population analysis (i.e. all locally advanced and metastatic patients) for degarelix were outside the range normally considered to be a cost-effective use of NHS resources based on their preferred assumptions, being: • Treatment continues until death based on clinical practise • No difference in treatment effect in terms of PSA progression or death • No difference in the rate of CV events for LHRH agonists vs degarelix • No difference in the rate of fractures for LHRH agonists vs degarelix • The most appropriate treatment comparator was 3 monthly triptorelin as this was the cheapest (although we note that the comparator should be chosen on the basis of established NHS practice [section 6.2.2. of the NICE Methods Guide] and not merely because it is the cheapest, particularly since triptorelin only has an 11% market share, compared to 31% and 27% share for the leading products in the market) Essentially the preferred assumptions assume no difference in treatment effect between degarelix and agonists other than rapid testosterone reduction, the benefits of which were only included in terms of reduction in rates of SCC based upon ITT analysis. These preferred assumptions resulted in an ICER of £103,179 per QALY based upon the best available evidence for the rate of SCC in the overall population of patients treated with LHRH agonists (Oh et al). The Committee acknowledges that Ferring was unable to submit cost-effectiveness analysis prior to the AC meeting within the subgroup of patients who would benefit from a rapid reduction in testosterone. There are 3 key assumptions made within the analyses presented based upon the ITT, which invalidate the resulting ICERs as useful for decision making. These are the assumption that: 1. ALL patients in the metastatic population require treatment with degarelix in order to identify the 0.96% of patients who experience SCC; UK clinicians indicate that a maximum of 20% of metastatic patients would require treatment with estimates ranging from 8 to 20% and the majority of clinicians estimating 10% of patients would require treatment. 2. survival within the population who would be treated (those representing a particularly poor prognosis subgroup) would have the same expected survival as the ITT population. This assumption is particularly impactful as the costs of treatment with degarelix vs LHRH are ongoing, whereas the upfront costs of SCC are substantial.	Comment noted. The FAD recommends degarelix as an option for treating advanced hormone-dependent prostate cancer in people with spinal metastases, only if the commissioner can achieve at least the same discounted drug cost as that available to the NHS in June 2016.

Consultee	Comment [sic]	Response

	3. there is no quality of life benefit of treatment with degarelix within the population who most benefit from a rapid reduction in testosterone.
	
	In order to address these concerns, an additional cost-effectiveness analysis is presented. This is provided for two populations in line with the evidence collected via the Delphi consultation process:
	• Patients who will benefit from a rapid reduction in testosterone
	  o Painful bony metastases
	  o High-volume bony metastases (≥4; with one outside the pelvic/spine region – based on the STAMPEDE/ CHAARTED trial definition)
	  o Ureteric obstruction
	  o High potential for spinal cord compression
	• Patients with pre-existing cardiovascular disease
	
	The benefits of degarelix in rapidly reducing testosterone are clearly based upon mechanism of action, proven within the clinical trials programme and clearly detailed in the product SPC[13]. The benefits of degarelix in terms of reduction in cardiovascular risk are less clear cut. As detailed in the Cardiovascular Effects section above, however, sufficient evidence is available and supporting clinical consensus is present to signal that substantial benefit may be possible for this important patient population.
	
	Methods
	
	The existing cost-effectiveness model has been substantially adapted to provide a simplified model focusing upon the benefits of degarelix in terms of rapid reduction in testosterone. In accordance with the appeal decision, only benefits related to the group of patients at risk of spinal cord compression are included. These include:
	• reduction in the rate of SCC
	• reduction in the length of stay associated with initial inpatient admission whilst treatment takes effect
	• increase in quality of life (as demonstrated in the more severe subgroups in CS21)
	
	Rate of SCC
	As noted by the ERG only one suitable source of evidence is available for the rate of spinal cord compression within the first 30 days of receiving LHRH agonist therapy (Oh et al[14]). This study reported a rate of 0.96% (15/1,566) for SCC occurring within the first 30 days of LHRH agonist therapy in men with metastatic disease; with no difference seen according to whether or not patients received anti-androgen therapy. In adjusted analysis, there was no decrease in odds of any event for treatment with an antiandrogen within 6 days (OR, 1.04, 95% CI, 0.78-1.40) or 7 days (OR, 0.95, 95% CI, 0.72-1.25) before LHRH agonist treatment.
	Similar to the ERG report, no data were found to contradict the assumption that the rate of short-term SCC in	

Consultee	Comment [sic]	Response

patients receiving degarelix is expected to be zero.

Proportion of patients expected to be treated with degarelix

Clinical consultation was carried out by Ferring to identify the group of patients who would benefit from a rapid reduction in testosterone. The results of this clinical consultation are presented in appendix A. Clinicians estimated that approximately 10% of patients would be identified as suitable for treatment with degarelix i.e. those like to benefit from a rapid reduction in testosterone; the range provided was 8 – 20%. This range is further supported by actual use in areas of England where degarelix is available in line with its licensed indications and has a 9% market share (IMS MAT Unit data to April 2015)

Life expectancy of patients within the group who are likely to benefit from a rapid reduction in testosterone

As stated at the appraisal committee meeting, the group of patients who are likely to benefit from a rapid reduction in testosterone have a substantially different (reduction) expected life expectancy compared to the overall population. The median life expectancy for patients with spinal metastases, who form the bulk of the group of interest, is 24 months (95% CI 21-28 months)[15]. This compares to an ITT estimate of 9 years. This is particularly important as most clinicians expect to treat with degarelix for a patient's lifetime, an ongoing cost which is linked to life expectancy, whereas much of the costs of the side effects of high testosterone are immediate acute episode costs.

Summary of efficacy parameters

Parameter	Base case value	Range tested	Source
Proportion of metastatic population experiencing SCC when treated with LHRH	0.96%	0.54% - 6.1%	Oh et al[14]; range based upon 95% CI from Oh et al assuming a beta distribution, upper bound from Ahmann et al
Proportion of metastatic population experiencing SCC when treated with degarelix	0%	0% – same as for LHRH	No observations of SCC have been reported with degarelix
Proportion of metastatic patients identified by clinicians as benefit from rapid reduction in testosterone flare	10%	8% - 20%	Clinical consultation
Life expectancy	2 years	1 – 9 years	Drzymalski et al, 2010[15]

Costs

As presented previously the cost of degarelix is approximately £725 per annum more than triptorelin (the cheapest LHRH agonist).

BNF Chemical name	Drug name	Cost of 1st cycle	Cost

Consultee	Comment [sic]	Response

Degarelix	Firmagon®	£260.00	£129.37
Triptorelin	Decapeptyl® (3monthly)	£72.07	£69.00
Average LHRH	All the drugs	£78.16	£75.09

Clinicians consulted expected that, for patients who initiate treatment in an inpatient setting, the rapid onset of testosterone reduction seen with degarelix would be expected to save between 3 and 7 bed days in hospital. In many patients, clinicians are unable to administer LHRH agonists immediately as a course of anti-androgens is required first. During this time the patient remains in hospital experiencing extreme pain, since no treatment of the underlying issue is being received.
The cost of one of these stays in hospital is approximately equivalent to 3 years of treatment with degarelix vs LHRH agonists.

Parameter	Base case value	Range tested	Source
Cost per hospital day	£422.45	Number of days tested	NHS reference costs, weighted average of non-elective short stays for Musculoskeletal Signs and Symptoms: HD26A, HD26B, HD26C
Mean number of days	5	0-7	Clinical consultation 0 lower bound presented as extreme conservative scenario. 7 days quoted in ACD page 49

Quality of life
During clinical consultation the quality of life benefit gained by a group of patients who have an urgent need for rapid reduction in testosterone, was constantly stressed by clinicians. As such the quality of life data available from clinical trial CS21 was re-analysed in two patient groups more representative of the types of patients who are being considered as eligible for treatment within this re-appraisal:

- Patients with PSA>50
- Patients with metastatic disease

In patients with PSA>50, a statistically and clinically significant difference in quality of life was demonstrated with degarelix vs LHRH agonists (n=741, difference of 0.08; p<0.001 using the McKenzie mapping algorithm preferred by the ERG; significant in all 4 mapping algorithms p<=0.01). Fewer patients with metastatic disease

Consultee	Comment [sic]	Response
	were available within the CS21 dataset n=556; however a trend towards a significant benefit with degarelix was still observed in 2 out of 4 mapping algorithms, including the McKenzie mapping algorithm. Full results of additional quality of life analysis are presented in Appendix G. The impact of the additional quality of life analysis is presented in scenario analysis. Within the model base case, the same HRQL is conservatively assumed for both treatment arms. This does not take into account the benefit of degarelix in rapid pain reduction, a factor that is frequently cited as a key therapeutic advantage in clinical practice. *Impacts of SCC* All other model parameters in terms of the impacts of SCC are as presented within the previous model with inputs based on the cost-effectiveness model presented by Lu et al. *Benefits of rapid testosterone reduction not included within the modelling* In accordance with the appeal decision, only benefits related to the group of patients at risk of spinal cord compression are included. Other groups of patients identified as likely to experience substantial benefit from rapid reduction in testosterone are: • patients with elevated ALP or abnormal LFTs (as anti-androgens can cause severe liver toxicities so flare cover is not possible) • patients with a CT scan showing blocked urethra / BOO (hydro-nephrosis or enlarged lymph nodes). These patients go into renal failure if testosterone is not brought down The potential benefit of flare reduction in these patients is not included in this analysis. These patients are included, however, in the patient numbers expected to receive degarelix estimated by the clinicians. This presents a highly conservative analysis that includes the cost of treating these patients without the associated benefit. *Pre-existing cardiovascular disease* In order to evaluate the impact of treatment with degarelix in patients with pre-existing cardiovascular disease, the original ERG base case was modified for use in this patient population and according to the Committee's preferred assumptions as follows: • 100% of patients assumed to have pre-existing cardiovascular disease • Equal PSA progression for LHRH agonists and degarelix • McKenzie algorithm for utilities • No costs or disutilities included for SCC or MSEs (in order to provide separate results for this patient population) **Results** Based upon the population of patients requiring rapid testosterone reduction treatment with degarelix is	

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>
dominant, with a cost saving of £968. The benefit of reduced hospital stay alone outweighs the entire additional treatment costs of degarelix.
Discounted cost-effectiveness results, base case analysis
<table>
<tr><th></th><th>Degarelix</th><th>Triptorelin</th><th>Avg. LHRH</th><th>Degarelix vs triptorelin</th><th>Degarelix vs Avg. LHRH</th></tr>
<tr><td>Probability of SCC</td><td>0.000</td><td>0.010</td><td>0.010</td><td>-0.010</td><td>-0.010</td></tr>
<tr><td>Drug costs</td><td>£3,131</td><td>£1,600</td><td>£1,742</td><td>£1,531</td><td>£1,390</td></tr>
<tr><td>Cost of SCCs</td><td>£0</td><td>£4,458</td><td>£4,458</td><td>-£4,458</td><td>-£4,458</td></tr>
<tr><td>Cost from increased hospital stay awaiting testosterone reduction</td><td>£0</td><td>£2,041</td><td>£2,041</td><td>-£2,041</td><td>-£2,041</td></tr>
<tr><td>Total cost</td><td>£3,131</td><td>£8,100</td><td>£8,241</td><td>-£4,968</td><td>-£5,110</td></tr>
<tr><td>QALYs</td><td>1.42</td><td>1.37</td><td>1.37</td><td>0.05</td><td>0.05</td></tr>
<tr><td>ICER</td><td></td><td></td><td></td><td>Dominant</td><td>Dominant</td></tr>
</table>

Scenario analysis
Scenario analysis results presented based upon the upper and lower bounds for each of the key model parameters discussed earlier are presented below. In all cases treatment with degarelix remains the dominant treatment option.
Pre-existing cardiovascular disease
Cost-effectiveness model results demonstrate that, based upon the best available evidence, degarelix is cost-effective in the sub-group of patients with pre-existing cardiovascular disease, with an ICER substantially below usual cost-effectiveness thresholds.
<table>
<tr><th rowspan="2">Treatment Arm</th><th colspan="3">Totals</th><th rowspan="2">Inc Costs</th><th rowspan="2">Inc QALYs</th><th rowspan="2">Inc Life Years</th><th rowspan="2">Cost per QALY</th><th rowspan="2">Cost per Life Year</th></tr>
<tr><th>Costs</th><th>QALYs</th><th>Life Years</th></tr>
<tr><td>Triptorelin 3 Monthly</td><td>£17,333</td><td>4.049</td><td>6.856</td><td></td><td></td><td></td><td>£10,371</td><td>£5,247</td></tr>
</table>
</td><td></td></tr>
</table>

Consultee	Comment [sic]	Response

Degarelix	£31,462	5.412	9.549	£14,129	1.362	2.69		

Conclusion

The ERG was unable to include the additional benefits of degarelix specific to this patient population, given that all previous modelling had been based on ITT analysis. The analyses presented here are nonetheless broadly in agreement with the ERGs conclusion that only a very low rate of SCC is required in the patient population treated with degarelix. UK clinicians are in agreement that there is a clearly definable place in therapy for degarelix in patients who require rapid reduction of testosterone. The use of degarelix in these patients is not only clinically effective due to its mechanism of action but it is also cost-effective due to increased short-term costs (acute hospital stays) and long-term costs associated with the adverse consequences of inability to swiftly reduce testosterone. Additionally degarelix is shown to be cost-effective based upon the best available evidence in the sub-group of patients with pre-existing cardiovascular disease. The cost effectiveness of degarelix in this subgroup is further enhanced by including the possible price reductions noted above:

Treatment Arm	**Totals**			**Inc. Costs**	**Inc. QALYs**	**Inc. Life Years**	**Cost per QALY**
	Costs	**QALYs**	**Life Years**				
10% reduction in the acquisition cost of degarelix							
Triptorelin 3 Monthly	£17,333	4.049	6.856				
Degarelix	£30,215	5.412	9.549	£12,882	1.362	2.69	£9,455
15% reduction in the acquisition cost of degarelix							
Triptorelin 3 Monthly	£17,333	4.049	6.856				
Degarelix	£29,592	5.412	9.549	£12,258	1.362	2.69	£8,998

Scenario	**Cost of degarelix**	**Cost of triptorelin**	**QALYs with degarelix**	**QALYs with triptorelin**	**Incremental costs**	**Incremental QALYs**	**ICER**
Base case	£3,131	£8,100	1.42	1.37	-£4,968	0.05	Dominant
8% requiring treatment	£3,131	£10,329	1.42	1.34	-£7,198	0.08	Dominant

Consultee	Comment [sic]	Response

20% requiring treatment	£3,131	£6,316	1.42	1.39	-£3,185	0.03	Dominant
0.54% SCC rate for LHRH	£3,131	£6,149	1.42	1.39	-£3,018	0.03	Dominant
6.1% SCC rate for LHRH	£3,131	£31,970	1.42	1.08	-£28,839	0.35	Dominant
0.48% SCC rate for degarelix	£5,360	£8,100	1.40	1.37	-£2,739	0.03	Dominant
Equal rate of SCC in degarelix vs LHRH	£7,590	£8,100	1.37	1.37	-£510	0.00	Dominant
1 year life expectancy	£1,657	£5,442	0.72	0.70	-£3,785	0.03	Dominant
9 years life expectancy	£12,147	£24,341	5.70	5.49	-£12,194	0.22	Dominant
0 days increased hospitalisation with LHRH	£3,131	£6,059	1.42	1.37	-£2,927	0.05	Dominant
7 days increased hospitalisation with LHRH	£3,131	£8,916	1.42	1.37	-£5,785	0.05	Dominant
HRQL benefit with degarelix as per PSA>50 group	£3,131	£8,100	1.57	1.37	-£4,968	0.20	Dominant
HRQL benefit with degarelix as per metastatic group	£3,131	£8,100	1.47	1.33	-£4,968	0.14	Dominant

Conclusions
Ferring believes that Degarelix does have a place in therapy and that this place is not widespread use as the Appraisal Committee perhaps fears. This place is with certain patient cohorts, namely those presenting with symptomatic and/or high-volume metastatic, hormone-dependent prostate cancer - characterised by any one of the following: painful bony metastases, high-volume bony metastases (≥4; with one outside the pelvic/spine region – based on the STAMPEDE/ CHAARTED trial definition), ureteric obstruction, systemic signs of cancer; e.g., weight loss, depression, anorexia, anaemia, high potential for spinal cord compression, pre-existing cardiovascular disease.

Consultee	Comment [sic]	Response
	Usage in these cohorts has been endorsed by clinicians through a Delphi consultation with 98.4% consensus amongst 61 clinicians (range 72% to 100% consensus). We would ask that the Committee takes this into account in its deliberations. The Scottish Medicines Consortium approved the use of degarelix in advanced prostate cancer following a full submission in 2010. The predicted uptake assumed a cumulative maximum impact at 5 years equivalent to 811 patients, based on the recommendation for use. Ferring has supported that place in the care pathway and the actual patient numbers have remained well within that threshold (Appendix C). The All Wales Medicines Strategy Group supported the use of degarelix in 2012 and patient numbers here too have remained well within the expected range. A Patient Access Scheme has supported the cost effectiveness of that use in both countries, as well as in some 50 CCGs & 5PCTs in England. Ferring's suggestions for a PAS in England were rejected by the Dept of Health due to the complexity of primary care finance and reimbursement arrangements. A National Rebate Scheme was set up through tender at the CMU and has been operating successfully across England for the last two years. Discussions are ongoing at the CMU to extend this arrangement to 2017 at the agreed discounted rate. Ferring appreciates the Committee's concern over usage creep and hence, despite the HE analyses demonstrating that degarelix is cost effective in the defined subgroups, Ferring commits to exploring options to reduce the acquisition price further at the point of a positive FAD being published. This is in addition to honouring the purchase price in existing rebates and contracts where they exist. Attached is recent testimony showing that with the national rebate scheme and wider access policy it is used appropriately and cost effectively.	

Comments received from clinical experts and patient experts

None received.

Comments received from commentators

None received.

Comments received from members of the public

Role*	Section	Comment [sic]	Response
NHS Professional	General	I have been using degarelix since its introduction in 2009 and to change practice of a well established drug with evidence based effectiveness and specific clinical indications is not good medical practice. It's use in the acute management of metastatic prostate cancer particularly for symptomatic men with bone pain, spinal cord compression or ureteric instruction is well established. My practice has always to switch men after a month or so to conventional ADT to minimise costs for the NHS. I do not support the recommendation from NICE and I believe patient care will be severely compromised and I don't believe the costs to be excessive compared to many oncology drugs in common use.	Comment noted. The FAD recommends degarelix as an option for treating advanced hormone-dependent prostate cancer in people with spinal metastases, only if the commissioner can achieve at least the same discounted drug cost as that available to the NHS in June 2016.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Response to ACD

Summary

Ferring appreciates this opportunity to address the recent ACD in respect of degarelix, to support our previous submission. We shall aim to demonstrate our belief, consistent with that of many expert clinicians in this field, that degarelix is a clinically effective option for the treatment of men with advanced, hormone-dependent prostate cancer in a defined subgroup and that it is cost-effective in this group.

We will address three key issues arising from the draft recommendation:

1. a clinically derived and workable definition for the sub group suitable for this treatment
2. a review of cost efficacy of antagonists over agonists in the sub group – taking into account the cost benefit of rapid symptom relief on hospital stay
3. pricing policy – Ferring is looking at mechanisms to reduce the acquisition cost of degarelix further in order to enhance the cost effectiveness to the NHS in the defined populations.

In providing this additional information, supporting results and clinical data, we seek a positive outcome from the Appraisal Committee that will benefit patients across England.

1. Sub group of patients suitable for treatment with degarelix.

Ferring convened an expert advisory board to address the challenge of developing a clear description of the specific, in-label patient population(s) that are most suitable for treatment with degarelix. The expert advisory board comprised six Urology Consultants from a range of units in England. Using a nominal group technique, the clinicians defined the symptomatic, diagnostic and differential elements of the patient groups they considered most suitable for treatment with degarelix. They graded the level of evidence that supported their decision and reached consensus on several defining characteristics.

The findings of the advisory board were tested in a two-round, web-based Delphi consultation (see Appendix A for methods and results). After removal of two experts who failed to meet the screening criteria for the consultation, a total of 61 experts participated in round 1, of which 47% (n=29) also completed round 2. At the time of the consultation, all Delphi panellists had direct clinical responsibility for patients with advanced hormone-dependent prostate cancer being treated with either degarelix or a luteinising hormone-releasing hormone (LHRH) agonist. The Delphi consultation reached consensus on the following universal descriptor:

Degarelix should be considered for patients presenting with symptomatic and/or high-volume metastatic, hormone-dependent prostate cancer – characterised by any one of the following;

- **painful bony metastases**
- **high-volume bony metastases (≥4; with one outside the pelvic/spine region – based on the STAMPEDE/ CHAARTED trial definition)**
- **ureteric obstruction**
- **systemic signs of cancer; eg, weight loss, depression, anorexia, anaemia**

- **high potential for spinal cord compression**
- **pre-existing cardiovascular disease**

On the basis of substantial validated clinical opinion and experience, Ferring would ask the Committee to accept this patient sub group in its consideration for recommendation.

In addition, consensus was reached on supporting statements for consideration in treatment, as follows:

- **LHRH antagonists are less cardiotoxic than LHRH agonists**
- **LHRH antagonists are less likely to cause undesirable, cardio-related consequences than LHRH agonists**
- **LHRH antagonists provide a more rapid control of serum testosterone levels than LHRH agonists, and, therefore, should be considered as a treatment option to control the acute symptoms related to advanced, hormone-dependent prostate cancer**

The above consensus statements support the second key issue addressed below.

2. Efficacy of Antagonists over Agonists

In the recent draft ACD recommendation there is an assumption that degarelix, a novel GnRH antagonist, is clinically the same as a LHRH agonist. However, we respectfully disagree with this assumption and we set out some of the key differences in the section below. We specifically wish to address the committee's interpretation of testosterone flare. The committee acknowledged that degarelix is particularly beneficial for avoiding testosterone flare, which may have led to the initial recommendation in the original ACD (pre-appeal) for use in patients at risk of spinal cord compression. Ferring appreciates the fact that the committee did attempt to find a sub-group where it could recommend degarelix. The focus on flare avoidance, however, is potentially misleading. The key benefit that degarelix offers is a rapid reduction in testosterone and other sex hormones such as FSH and LH[2]. This suggests optimum use of degarelix in patients who present with bone pain, bladder outlet/ureteric obstruction, lumbar back pain and hydronephrosis. By contrast, to use an agonist in this situation would result in a **7 to 10 day delay** whilst an anti-androgen can take effect, leading to a possible increased risk of complications, a poorer quality of life, additional hospital bed occupancy and potential adverse consequences such as spinal cord compression and bladder outlet/ureteric obstruction. The Committee did in fact note that Ferring were not given the opportunity to present a cost-effectiveness case at the last appraisal committee meeting in patients who would benefit from a rapid reduction in testosterone (page 60 of the AC document). This cost-effectiveness case is therefore presented within this response. In accordance with the appeal decision, only benefits that are related to the group of patients at risk of spinal cord compression are included. These include:

- reduction in the rate of SCC
- reduction in the length of stay associated with initial inpatient admission whilst treatment takes effect
- increase in quality of life (as demonstrated in the more severe subgroups in CS21).

The resulting cost-effectiveness analysis demonstrates that in the subgroup of patients who would be treated with degarelix in clinical practice (i.e. those patients for whom a rapid reduction in

testosterone would be beneficial) degarelix is highly cost-effective, proving to be dominant in all clinically realistic scenarios (see appendix B).

Ferring maintains that there are differences in the associated cardiovascular risk for patients being treated with agonists compared to degarelix. Our feeling is that the evidence on this has been given insufficient weight, perhaps due to the fact that the evidence for agonists causing a problem was not considered in the original review, the belief that cardiovascular issues are caused by metabolic changes over the longer term due to androgen deprivation and also due to a (mis)interpretation that degarelix is cardio-protective. By considering the data that support an effect of agonist treatment on the incidence of CV events, this in turn helps to explain the relative risk reduction that has been observed with degarelix. This effect is a significantly reduced risk, particularly in the short term rather than because degarelix inherently lowers the risk, in the manner, say of a statin. Hence why the reduction in risk is observed in the first year.

3. Pricing Policy

Despite the fact that a universal rebate is offered by Ferring and is in operation across the NHS, the current health economic modelling has been conducted on the existing trade price for degarelix. Unfortunately, due to the peculiarities of the NHS transactional flow in primary care, the Department of Health was unable to approve the Patient Access Scheme accepted by, and used in, Scotland and Wales. Ferring is currently pursuing options to reduce the acquisition price of degarelix and asks that the Committee acknowledge these options, and make a supportive recommendation, subject to achieving a target acquisition cost of between £221 - £234 for the initiation dose and £109.96 - £116.43 for the maintenance dose, to commence at publication of the FAD (we note a similar approach was taken in the NICE technology appraisal recommendations for drug-eluting stents). These prices have been modelled through the revised HE models and are presented for reference in appendix F.

Ferring is exploring different options to achieve these target prices, which include - but are not limited to - the following:

- Simple price reduction
- Price reduction and free starter pack to hospitals
- Discount applied to packs delivered directly by a home care company or wholesaler, either to the GP practise or patient's home
- CMU tender.

Additionally the discounted price offered via the existing national tender in place at the CMU and any existing CCG contracts will be honoured.

Other key differences between GnRH Antagonist and LHRH Agonists

Role of s-ALP and rate of fractures

There was an assumption that fractures would increase over time for both therapies, given that ADT leads to a reduction in bone mineral density. This ignores the evidence from Schroder et al[3] that demonstrates that serum alkaline phosphatase, a well-established endpoint with large predictive value for several cancer forms that metastasise to the skeleton, is controlled better and for longer in

degarelix compared to an agonist. Better control of cancer activity in the bone would lead to a reduction in pathological fractures. The ERG stated that the results should be interpreted with caution because "only the statistically significant finding from a post-hoc subgroup analysis of patients with metastatic disease was reported" (section 3.25) and that baseline characteristics were not presented.

This is contrary to the data:

- High S-ALP can only be present in patients with metastatic disease and indeed bone metastases
- Baseline characteristics are presented in the paper published by Schroder et al 2010[3]

The introduction of new therapies for late-stage prostate cancer like cytotoxic therapy, abiraterone or enzalutamide has again shown the value of S-ALP as a measure of disease volume within the skeleton and also as a prognostic marker[4, 16]. S-ALP has a value independent of, and superior to PSA, in many patients with advanced skeletal metastasis. Schroder et al 2010 [(3)] shows the better ALP suppression of degarelix compared with leuprolide and Klotz et al 2014 [(2)] confirms this. Patients without skeletal metastasis don't have elevated PSA and don't show an ALP response to treatment and serve as good control groups. Schroder et al 2010[3] showed that the superiority of degarelix is greater when there is more disease in the skeleton illustrated in the patients with low Hb (<13 g/dL).

These groups also represent patients where the negatives/dangers of surge/flare are the greatest. The agonists are even contraindicated in the most advanced groups. A serious warning is issued for agonists due to surge/flare[5,6,7]. Patients in these groups would need to have surgical orchidectomy or have a surge during agonist treatment w/wo antiandrogens if degarelix is not available. This lack of an appropriate medical treatment would potentially cause considerable harm.

Cardiovascular effects

The lack of the effect of Degarelix on serious cardiovascular events was not given the prominence it perhaps deserves based on 3 main assumptions:

- The increase in conventional cardiovascular risk factors was due to androgen deprivation (section 4.10) – changes in blood lipids, increased plasma insulin levels & increased risk of metabolic syndrome – hence there would be no difference between Degarelix and an agonist as both lower testosterone to the same level
- The paper by Albertsen et al[8] was a pooled analysis and hypothesis generating only
- The belief that Albertsen results were driven mainly by the inclusion of one small study that showed a relative risk reduction of 80% which was felt to be implausible

In addressing the points above:

If the difference in CV events was purely driven by ADT then it would be reasonable to assume that an agonist would have the same effect as bilateral orchiectomy.

However, several large studies have highlighted a clear difference in associated risk of CHD, MI & sudden cardiac death in patients treated with LHRH agonists compared to orchiectomy (Keating

2006[9], Gandaglia 2010[10]). It would be unreasonable therefore to conclude that increased CV risk is solely down to ADT.

These data were not considered fully by the committee in reaching their conclusion.

Agonists increase the risk of a thromboembolic event (MI etc) in the shorter term (Gandaglia[10]). There is no evidence, however, to suggest that antagonists increase that risk. Indeed the FDA published the following statement in October 2010:

"The U.S. Food and Drug Administration (FDA) has notified the manufacturers of the Gonadotropin-Releasing Hormone (GnRH) agonists of the need to add new safety information to the Warnings and Precautions *section of the drug labels. This new information warns about increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke) in men receiving these medications for the treatment of prostate cancer."*

Underlying risk is also driven by the presence of pre-existing CV disease. A plausible explanation of how antagonists avoid risk appears to have been misinterpreted by the Committee which refers to "degarelix's potential effect of reducing inflammation linked with atherosclerosis". Degarelix does not claimed to reduce inflammation or to be a secondary prevention therapy; it simply does not exacerbate the risk to the same extent.

Albertsen[8] results were presented both as the original pooled analysis and as a meta-analysis. In both analyses a statistical difference was observed between Degarelix and the agonist in terms of overall risk – favouring degarelix. By focussing solely on Albertsen[8], though, the Committee is ignoring the evidence referred to above that demonstrates the negative impact that agonist therapy has on CV risk and that led to a warning being issued by the FDA[11].

The results of 3 key studies drive the overall result of Albertsen[8] and all favour degarelix. The 80% relative risk reduction observed in one of these may have been misinterpreted by the committee. If Degarelix was considered to be cardioprotective then the 80% RRR would seem incredible given that statins only reduce relative risk by up to 40%[12]. **However, Degarelix is not cardioprotective and should not be interpreted as such.** The apparent relative risk reduction is driven by the level to which the agonist increases risk and it is the significantly lower risk of degarelix that drives the relative reduction.

Health Economic Assessment

Context

Overall the Committee concluded that the ICERs presented by the ERG based upon ITT population analysis (i.e. all locally advanced and metastatic patients) for degarelix were outside the range normally considered to be a cost-effective use of NHS resources based on their preferred assumptions, being:

- Treatment continues until death based on clinical practise
- No difference in treatment effect in terms of PSA progression or death
- No difference in the rate of CV events for LHRH agonists vs degarelix
- No difference in the rate of fractures for LHRH agonists vs degarelix
- The most appropriate treatment comparator was 3 monthly triptorelin as this was the cheapest (although we note that the comparator should be chosen on the basis of

established NHS practice [section 6.2.2. of the NICE Methods Guide] and not merely because it is the cheapest, particularly since triptorelin only has an 11% market share, compared to 31% and 27% share for the leading products in the market)

Essentially the preferred assumptions assume no difference in treatment effect between degarelix and agonists other than rapid testosterone reduction, the benefits of which were only included in terms of reduction in rates of SCC based upon ITT analysis.

These preferred assumptions resulted in an ICER of £103,179 per QALY based upon the best available evidence for the rate of SCC in the overall population of patients treated with LHRH agonists (Oh et al).

The Committee acknowledges that Ferring was unable to submit cost-effectiveness analysis prior to the AC meeting within the subgroup of patients who would benefit from a rapid reduction in testosterone. There are 3 key assumptions made within the analyses presented based upon the ITT, which invalidate the resulting ICERs as useful for decision making. These are the assumption that:

1. ALL patients in the metastatic population require treatment with degarelix in order to identify the 0.96% of patients who experience SCC; UK clinicians indicate that a maximum of 20% of metastatic patients would require treatment with estimates ranging from 8 to 20% and the majority of clinicians estimating 10% of patients would require treatment.
2. survival within the population who would be treated (those representing a particularly poor prognosis subgroup) would have the same expected survival as the ITT population. This assumption is particularly impactful as the costs of treatment with degarelix vs LHRH are ongoing, whereas the upfront costs of SCC are substantial.
3. there is no quality of life benefit of treatment with degarelix within the population who most benefit from a rapid reduction in testosterone.

In order to address these concerns, an additional cost-effectiveness analysis is presented. This is provided for two populations in line with the evidence collected via the Delphi consultation process:

- Patients who will benefit from a rapid reduction in testosterone
    - Painful bony metastases
    - High-volume bony metastases (≥4; with one outside the pelvic/spine region – based on the STAMPEDE/ CHAARTED trial definition)
    - Ureteric obstruction
    - High potential for spinal cord compression
- Patients with pre-existing cardiovascular disease

The benefits of degarelix in rapidly reducing testosterone are clearly based upon mechanism of action, proven within the clinical trials programme and clearly detailed in the product SPC[13]. The benefits of degarelix in terms of reduction in cardiovascular risk are less clear cut. As detailed in the Cardiovascular Effects section above, however, sufficient evidence is available and supporting clinical consensus is present to signal that substantial benefit may be possible for this important patient population.

Methods

The existing cost-effectiveness model has been substantially adapted to provide a simplified model focusing upon the benefits of degarelix in terms of rapid reduction in testosterone. In accordance with the appeal decision, only benefits related to the group of patients at risk of spinal cord compression are included. These include:

- reduction in the rate of SCC
- reduction in the length of stay associated with initial inpatient admission whilst treatment takes effect
- increase in quality of life (as demonstrated in the more severe subgroups in CS21)

Rate of SCC

As noted by the ERG only one suitable source of evidence is available for the rate of spinal cord compression within the first 30 days of receiving LHRH agonist therapy (Oh et al[14]). This study reported a rate of 0.96% (15/1,566) for SCC occurring within the first 30 days of LHRH agonist therapy in men with metastatic disease; with no difference seen according to whether or not patients received anti-androgen therapy. In adjusted analysis, there was no decrease in odds of any event for treatment with an antiandrogen within 6 days (OR, 1.04, 95% CI, 0.78-1.40) or 7 days (OR, 0.95, 95% CI, 0.72-1.25) before LHRH agonist treatment.

Similar to the ERG report, no data were found to contradict the assumption that the rate of short-term SCC in patients receiving degarelix is expected to be zero.

Proportion of patients expected to be treated with degarelix

Clinical consultation was carried out by Ferring to identify the group of patients who would benefit from a rapid reduction in testosterone. The results of this clinical consultation are presented in appendix A. Clinicians estimated that approximately 10% of patients would be identified as suitable for treatment with degarelix i.e. those like to benefit from a rapid reduction in testosterone; the range provided was 8 – 20%. This range is further supported by actual use in areas of England where degarelix is available in line with its licensed indications and has a 9% market share (IMS MAT Unit data to April 2015)

Life expectancy of patients within the group who are likely to benefit from a rapid reduction in testosterone

As stated at the appraisal committee meeting, the group of patients who are likely to benefit from a rapid reduction in testosterone have a substantially different (reduction) expected life expectancy compared to the overall population. The median life expectancy for patients with spinal metastases, who form the bulk of the group of interest, is 24 months (95% CI 21-28 months)[15]. This compares to an ITT estimate of 9 years. This is particularly important as most clinicians expect to treat with degarelix for a patient's lifetime, an ongoing cost which is linked to life expectancy, whereas much of the costs of the side effects of high testosterone are immediate acute episode costs.

Summary of efficacy parameters

Parameter	Base case value	Range tested	Source
Proportion of metastatic population experiencing SCC when treated with LHRH	0.96%	0.54% - 6.1%	Oh et al[14]; range based upon 95% CI from Oh et al assuming a beta distribution, upper bound from Ahmann et al
Proportion of metastatic population experiencing SCC when treated with degarelix	0%	0% – same as for LHRH	No observations of SCC have been reported with degarelix
Proportion of metastatic patients identified by clinicians as benefit from rapid reduction in testosterone flare	10%	8% - 20%	Clinical consultation
Life expectancy	2 years	1 – 9 years	Drzymalski et al, 2010[15]

Costs

As presented previously the cost of degarelix is approximately £725 per annum more than triptorelin (the cheapest LHRH agonist).

BNF Chemical name	Drug name	Cost of 1st cycle	Cost for each subsequent cycle
Degarelix	Firmagon®	£260.00	£129.37
Triptorelin	Decapeptyl® (3monthly)	£72.07	£69.00
Average LHRH	All the drugs	£78.16	£75.09

Clinicians consulted expected that, for patients who initiate treatment in an inpatient setting, the rapid onset of testosterone reduction seen with degarelix would be expected to save between 3 and 7 bed days in hospital. In many patients, clinicians are unable to administer LHRH agonists immediately as a course of anti-androgens is required first. During this time the patient remains in hospital experiencing extreme pain, since no treatment of the underlying issue is being received.

The cost of one of these stays in hospital is approximately equivalent to 3 years of treatment with degarelix vs LHRH agonists.

Parameter	Base case value	Range tested	Source
Cost per hospital day	£422.45	Number of days tested	NHS reference costs, weighted average of non-elective short stays for Musculoskeletal Signs and Symptoms: HD26A, HD26B, HD26C
Mean number of days	5	0-7	Clinical consultation 0 lower bound presented as extreme conservative scenario. 7 days quoted in ACD page 49

Quality of life

During clinical consultation the quality of life benefit gained by a group of patients who have an urgent need for rapid reduction in testosterone, was constantly stressed by clinicians. As such the quality of life data available from clinical trial CS21 was re-analysed in two patient groups more representative of the types of patients who are being considered as eligible for treatment within this re-appraisal:

- Patients with PSA>50
- Patients with metastatic disease

In patients with PSA>50, a statistically and clinically significant difference in quality of life was demonstrated with degarelix vs LHRH agonists (n=741, difference of 0.08; $p<0.001$ using the McKenzie mapping algorithm preferred by the ERG; significant in all 4 mapping algorithms $p<=0.01$). Fewer patients with metastatic disease were available within the CS21 dataset n=556; however a trend towards a significant benefit with degarelix was still observed in 2 out of 4 mapping algorithms, including the McKenzie mapping algorithm. Full results of additional quality of life analysis are presented in Appendix G.

The impact of the additional quality of life analysis is presented in scenario analysis. Within the model base case, the same HRQL is conservatively assumed for both treatment arms. This does not take into account the benefit of degarelix in rapid pain reduction, a factor that is frequently cited as a key therapeutic advantage in clinical practice.

Impacts of SCC

All other model parameters in terms of the impacts of SCC are as presented within the previous model with inputs based on the cost-effectiveness model presented by Lu et al.

Benefits of rapid testosterone reduction not included within the modelling

In accordance with the appeal decision, only benefits related to the group of patients at risk of spinal cord compression are included. Other groups of patients identified as likely to experience substantial benefit from rapid reduction in testosterone are:

- patients with elevated ALP or abnormal LFTs (as anti-androgens can cause severe liver toxicities so flare cover is not possible)
- patients with a CT scan showing blocked urethra / BOO (hydro-nephrosis or enlarged lymph nodes). These patients go into renal failure if testosterone is not brought down

The potential benefit of flare reduction in these patients is not included in this analysis. These patients are included, however, in the patient numbers expected to receive degarelix estimated by the clinicians. This presents a highly conservative analysis that includes the cost of treating these patients without the associated benefit.

Pre-existing cardiovascular disease

In order to evaluate the impact of treatment with degarelix in patients with pre-existing cardiovascular disease, the original ERG base case was modified for use in this patient population and according to the Committee's preferred assumptions as follows:

- 100% of patients assumed to have pre-existing cardiovascular disease
- Equal PSA progression for LHRH agonists and degarelix
- McKenzie algorithm for utilities
- No costs or disutilities included for SCC or MSEs (in order to provide separate results for this patient population)

Results

Based upon the population of patients requiring rapid testosterone reduction treatment with degarelix is dominant, with a cost saving of £968. The benefit of reduced hospital stay alone outweighs the entire additional treatment costs of degarelix.

Discounted cost-effectiveness results, base case analysis

	Degarelix	**Triptorelin**	**Avg. LHRH**	**Degarelix vs triptorelin**	**Degarelix vs Avg. LHRH**
Probability of SCC	0.000	0.010	0.010	-0.010	-0.010
Drug costs	£3,131	£1,600	£1,742	£1,531	£1,390
Cost of SCCs	£0	£4,458	£4,458	-£4,458	-£4,458
Cost from increased hospital stay awaiting testosterone reduction	£0	£2,041	£2,041	-£2,041	-£2,041
Total cost	£3,131	£8,100	£8,241	-£4,968	-£5,110
QALYs	1.42	1.37	1.37	0.05	0.05
ICER				Dominant	Dominant

Scenario analysis

Scenario analysis results presented based upon the upper and lower bounds for each of the key model parameters discussed earlier are presented below. In all cases treatment with degarelix remains the dominant treatment option.

Pre-existing cardiovascular disease

Cost-effectiveness model results demonstrate that, based upon the best available evidence, degarelix is cost-effective in the sub-group of patients with pre-existing cardiovascular disease, with an ICER substantially below usual cost-effectiveness thresholds.

Treatment Arm	Totals			Inc Costs	Inc QALYs	Inc Life Years	Cost per QALY	Cost per Life Year
	Costs	QALYs	Life Years					
Triptorelin 3 Monthly	£17,333	4.049	6.856				£10,371	£5,247
Degarelix	£31,462	5.412	9.549	£14,129	1.362	2.69		

Conclusion

The ERG was unable to include the additional benefits of degarelix specific to this patient population, given that all previous modelling had been based on ITT analysis. The analyses presented here are nonetheless broadly in agreement with the ERGs conclusion that only a very low rate of SCC is required in the patient population treated with degarelix. UK clinicians are in agreement that there is a clearly definable place in therapy for degarelix in patients who require rapid reduction of testosterone. The use of degarelix in these patients is not only clinically effective due to its mechanism of action but it is also cost-effective due to increased short-term costs (acute hospital stays) and long-term costs associated with the adverse consequences of inability to swiftly reduce testosterone. Additionally degarelix is shown to be cost-effective based upon the best available evidence in the sub-group of patients with pre-existing cardiovascular disease. The cost effectiveness of degarelix in this subgroup is further enhanced by including the possible price reductions noted above:

Treatment Arm	Totals			Inc. Costs	Inc. QALYs	Inc. Life Years	Cost per QALY
	Costs	QALYs	Life Years				
10% reduction in the acquisition cost of degarelix							
Triptorelin 3 Monthly	£17,333	4.049	6.856				
Degarelix	£30,215	5.412	9.549	£12,882	1.362	2.69	£9,455
15% reduction in the acquisition cost of degarelix							
Triptorelin 3 Monthly	£17,333	4.049	6.856				
Degarelix	£29,592	5.412	9.549	£12,258	1.362	2.69	£8,998

ERG Base Case Model - pre existing CV disease (model 1)

Base Case

Treatment Arm	Totals			Incremental Costs	Incremental QALY Gained	Incremental Life Years Gained	Cost per QALY
	Costs	QALYs Gained	Life Years Gained				
Triptorelin 3 Monthly (Decapeptyl)	£17,333	4.049	6.856				
Degarelix	£31,462	5.412	9.549	£14,129	1.362	2.69	**£10,371**

10% Cost Discount

Treatment Arm	Totals			Incremental Costs	Incremental QALY Gained	Incremental Life Years Gained	Cost per QALY
	Costs	QALYs Gained	Life Years Gained				
Triptorelin 3 Monthly (Decapeptyl)	£17,333	4.049	6.856				
Degarelix	£30,215	5.412	9.549	£12,882	1.362	2.69	**£9,455**

15% Cost Discount

Treatment Arm	Totals			Incremental Costs	Incremental QALY Gained	Incremental Life Years Gained	Cost per QALY
	Costs	QALYs Gained	Life Years Gained				
Triptorelin 3 Monthly (Decapeptyl)	£17,333	4.049	6.856				
Degarelix	£29,592	5.412	9.549	£12,258	1.362	2.69	**£8,998**

Scenario	Cost of degarelix	Cost of triptorelin	QALYs with degarelix	QALYs with triptorelin	Incremental costs	Incremental QALYs	ICER
Base case	£3,131	£8,100	1.42	1.37	-£4,968	0.05	Dominant
8% requiring treatment	£3,131	£10,329	1.42	1.34	-£7,198	0.08	Dominant
20% requiring treatment	£3,131	£6,316	1.42	1.39	-£3,185	0.03	Dominant
0.54% SCC rate for LHRH	£3,131	£6,149	1.42	1.39	-£3,018	0.03	Dominant
6.1% SCC rate for LHRH	£3,131	£31,970	1.42	1.08	-£28,839	0.35	Dominant
0.48% SCC rate for degarelix	£5,360	£8,100	1.40	1.37	-£2,739	0.03	Dominant
Equal rate of SCC in degarelix vs LHRH	£7,590	£8,100	1.37	1.37	-£510	0.00	Dominant
1 year life expectancy	£1,657	£5,442	0.72	0.70	-£3,785	0.03	Dominant
9 years life expectancy	£12,147	£24,341	5.70	5.49	-£12,194	0.22	Dominant
0 days increased hospitalisation with LHRH	£3,131	£6,059	1.42	1.37	-£2,927	0.05	Dominant
7 days increased hospitalisation with LHRH	£3,131	£8,916	1.42	1.37	-£5,785	0.05	Dominant
HRQL benefit with degarelix as per PSA>50 group	£3,131	£8,100	1.57	1.37	-£4,968	0.20	Dominant
HRQL benefit with degarelix as per metastatic group	£3,131	£8,100	1.47	1.33	-£4,968	0.14	Dominant

Conclusions

Ferring believes that Degarelix does have a place in therapy and that this place is not widespread use as the Appraisal Committee perhaps fears. This place is with certain patient cohorts, namely **those presenting with symptomatic and/or high-volume metastatic, hormone-dependent prostate cancer** - characterised by any one of the following: **painful bony metastases, high-volume bony metastases (≥4; with one outside the pelvic/spine region – based on the STAMPEDE/ CHAARTED trial definition), ureteric obstruction, systemic signs of cancer; e.g., weight loss, depression, anorexia, anaemia, high potential for spinal cord compression, pre-existing cardiovascular disease.**

Usage in these cohorts has been endorsed by clinicians through a Delphi consultation with 98.4% consensus amongst 61 clinicians (range 72% to 100% consensus). We would ask that the Committee takes this into account in its deliberations.

The Scottish Medicines Consortium approved the use of degarelix in advanced prostate cancer following a full submission in 2010. The predicted uptake assumed a cumulative maximum impact at 5 years equivalent to 811 patients, based on the recommendation for use. Ferring has supported that place in the care pathway and the actual patient numbers have remained well within that threshold (Appendix C).

The All Wales Medicines Strategy Group supported the use of degarelix in 2012 and patient numbers here too have remained well within the expected range.

A Patient Access Scheme has supported the cost effectiveness of that use in both countries, as well as in some 50 CCGs & 5PCTs in England.

Ferring's suggestions for a PAS in England were rejected by the Dept of Health due to the complexity of primary care finance and reimbursement arrangements. A National Rebate Scheme was set up through tender at the CMU and has been operating successfully across England for the last two years. Discussions are ongoing at the CMU to extend this arrangement to 2017 at the agreed discounted rate.

Ferring appreciates the Committee's concern over usage creep and hence, despite the HE analyses demonstrating that degarelix is cost effective in the defined subgroups, Ferring commits to exploring options to reduce the acquisition price further at the point of a positive FAD being published. This is in addition to honouring the purchase price in existing rebates and contracts where they exist.

Attached is recent testimony showing that with the national rebate scheme and wider access policy it is used appropriately and cost effectively.

Appendices

A. Delphi Panel Report
B. Cost efficacy models
C. Scottish usage data
D. CMU confirmation email
E. Testimonial for current rebate scheme
F. HE outputs at discounted rates
G. QoL supporting data

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Kate Moore
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24 June 2015

Dear Ms Moore,

Re: Single Technology Appraisal (STA) – degarelix for treating advanced, hormone-dependent prostate cancer: appraisal consultation document 2

Thank you for giving Prostate Cancer UK the opportunity to respond to NICE's appraisal consultation document 2 (ACD2) on degarelix for treating advanced, hormone-dependent prostate cancer.

About us

Prostate Cancer UK is the UK's leading charity for men with prostate cancer and prostate problems. We support men and provide information, find answers through funding research and lead change to raise awareness and improve care. The charity is committed to ensuring the voice of men with prostate cancer is at the heart of all we do.

Consultation response

1. **Has all of the relevant evidence been taken into account?**

   No.

   One of the key contributing factors to NICE's draft decision not to recommend degarelix within its marketing authorisation for treating advanced hormone-dependent prostate cancer was an inability to define and quantify the patient subgroup for which degarelix would be the optimal treatment.

   Clinical experts advised the Appraisal Committee that degarelix is particularly appropriate for men at high risk of disease progression. This patient subgroup was defined as those with a prostate specific antigen (PSA) level of more that 20 ng/ml, older men, those with pre-existing cardiovascular disease, and those with spinal metastases.

   NICE clinical guideline 175, Prostate cancer: Diagnosis and treatment, recommends bilateral orchidectomy as an alternative to continuous luteinizing hormone-releasing hormone (LHRH) agonist therapy (1). The Appraisal Committee does not appear to have considered quantifying the subgroup of patients using Hospital Episode Statistics (HES) data on bilateral orchidectomy. Bilateral orchidectomy rates may be an indicator of

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treatment for those men who are unsuitable for treatment with LHRH agonists and therefore use of this data could be used to quantify the subgroup for which degarelix would be a valuable treatment option.

In addition, the Appraisal Committee does not appear to have considered analysing rates of diagnosis for high-burden disease. This could be achieved by analysing PSA levels at diagnosis, although it would not provide information on men who go on to develop advanced prostate cancer..

2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No.

According to the British National Formulary (BNF), a starting dose of degarelix (Firmagon®) (240mg administered as two 120mg/3mL subcutaneous injections) costs £260 at list price. Subsequent maintenance doses (80mg/4mL administered as one subcutaneous injection every month) cost £129.37 at list price (2). At its list price, the total annual cost of degarelix is £1,683 in the first year and £1,552 thereafter.

This compares to an average annual cost of £953 (range = £760-£1,324), plus a three-week anti-androgen course averaging £26 (range = £6-£55), for currently available LHRH agonists (2).

At its list price, degarelix costs an average £704 more per patient in its first year and £573 more thereafter, compared with the average annual cost of treating a patient with a currently available LHRH agonist. We do not consider this to be a significant cost difference in relation to the benefit men who are unsuitable for LHRH agonists would gain from treatment with degarelix.

Furthermore, NICE clinical guideline 175 recommends bilateral orchidectomy as an alternative to continuous LHRH agonist therapy (1). We understand the approximate cost of a bilateral orchidectomy is £1,000[1]. Although this is a lower cost treatment, the physical and emotional impact of such an operation on men should not be under-estimated.

Finally, we believe that the manufacturer's proposed Patient Access Scheme (PAS) should be accepted by NICE, as it has been in Scotland (3) and Wales (4), to ensure the best value for the NHS.

3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

No.

According to NICE clinical guideline 175, the only active treatment alternative to continuous LHRH agonist therapy that can currently be offered to men with metastatic prostate cancer is bilateral orchidectomy (1). This is an undesirable alternative treatment option for many men who are unable to receive continuous LHRH agonists due to its irreversibility and the consideration of the impact of major surgery on recovery, as well as its emotional impacts. Degarelix is, therefore, an important treatment option that should be made available to appropriate men on the NHS.

[1] Figure from correspondence with the President of the British Association of Urological Surgeons (BAUS).

4. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?**

   Yes.

   The proposed recommendations would be of detriment to the care of older men.

   Clinical experts advised the Appraisal Committee that degarelix would be particularly appropriate for older men. Older men with prostate cancer are significantly less likely to undergo surgical procedures as part of their treatment (5,6). With bilateral orchidectomy as the only alternative active treatment option for men unsuitable for LHRH agonists, treatment options are therefore severely limited for older men at this stage of the prostate cancer treatment pathway. We believe degarelix should be available for these men.

Thank you again for this opportunity to respond to NICE's ACD2 on degarelix depot for treating advanced, hormone-dependent prostate cancer. Please do not hesitate to contact me if you have any further questions.

Yours sincerely,

[redacted], Prostate Cancer UK

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Response from The British Association of Urological Surgeons to ACD for Prostate cancer (advanced, hormone dependent) - degarelix depot [ID590]

In the view of BAUS, the conclusion of this draft ACD for ID590 not to use Degarelix for any indication is disappointing. BAUS feels Degarelix should be approved by NICE for use in the emergency setting of spinal cord compression (bearing in mind the difficulties in identifying patients at risk of SCC, the indication may be restricted to established spinal cord compression [SCC]) and bilateral ureteric obstruction due to hormone-naïve prostate cancer. The rapid achievement of a castrate testosterone in this group of patients should make it the drug of choice and equivalent to bilateral orchidectomy. It is well-established that most advanced prostate cancer patients prefer medical treatment to bilateral orchidectomy.

Standard methods of medical androgen deprivation take 4 weeks to achieve castrate testosterone, during which time disease may progress causing further irreversible clinical deterioration. Continuation of long-term androgen deprivation therapy in these patients could be using LHRH analogues unless the difference in cost between these drugs becomes insignificant; current evidence for superiority of degarelix over LHRH-analogues in terms of prolonged time to disease progression and reduction in cardiovascular disease risk is not above criticism and more robust evidence is awaited.

BAUS – 25 June 2015

23 June 2015

Response from the British Uro-oncology Group (BUG) to:

Appraisal consultation document

Degarelix for treating advanced hormone-dependent prostate cancer

On behalf of the British Uro-oncology Group (BUG), we would like to document our extreme disappointment over the ACD proposal that:

1.1 Degarelix is not recommended within its marketing authorisation for treating advanced hormone-dependent prostate cancer.

and urge NICE to reconsider this position.

We would propose that degarelix should be available as an option for:

- **men with high volume advanced (metastatic) disease who will benefit from immediate therapy with rapid reduction to testosterone and will avoid catastrophic consequences of any tumour flare eg spinal cord compression**

There is enthusiasm to have the opportunity to prescribe degarelix amongst oncologists and urologists who treat prostate cancer. This latest ACD decision is extremely disappointing for clinicians and patients who are suffering with advanced prostate cancer.

We appreciate that the amiable data are not all Level 1 evidence and that some of the articles are looking at post hoc analyses, pooled data and subgroups. However, there are consistently strong signals from all these studies that when considered together add up to providing convincing evidence that degarelix could be a more effective drug in terms of delaying the time to a castrate resistant state and is also safer with less risk of cardiovascular events and death. For these reasons we feel that clinicians should have the choice to prescribe the most effective drug at the initial stages of the disease, particularly if this can reduce cardiovascular disease progression – the consequences for the patient and the financial implications.

The evidence from the pivotal CS21 study entitled: Efficacy and Safety of Degarelix: a 12 month, comparative, randomised, open-label, parallel-group phase III study in patients with prostate cancer, Klotz L et al. BJUI 2008, demonstrated the non inferiority of degarelix in addition to immediate biochemical and clinical effectiveness without flare or the need for any additional flare protection. Degarelix was shown to achieve immediate testosterone reduction with a rapid PSA decrease and faster control of prostate cancer. The very low testosterone levels were maintained with degarelix.

Degarelix was shown to be a well-tolerated alternative to LHRH agonists with a good safety profile.

There have been some previous discussions over the fact that only 11% of men received an antiandrogen to prevent initial testosterone flare. The use of an antiandrogen does not totally block testosterone and the data comparing LHRH agonists to orchidectomy show some inconsistencies and it would appear that even when an antiandrogen is prescribed, this does not achieve total blockade of testosterone. The fact that whether an antiandrogen was administered or not with the initial injection does not prevent the ongoing testosterone miniflares and surges with subsequent injections. It is very possible that the immediate and continued superior suppression of testosterone accounts for the increased efficacy of degarelix seen in the post hoc analyses.

The data from further analyses show consistent signals to suggest that degarelix is a potentially more effective choice especially for men with high risk advanced (metastatic) prostate cancer.

1. Degarelix also demonstrates a more rapid and sustained suppression of FSH than LHRH agonists (CS21) and a further reduction of FSH was demonstrated in the crossover study when men treated with leuprorelin were changed to degarelix (CS21A). FSH is thought to have an impact on prostate cancer progression and has been shown to stimulate the growth of PC3 prostate cancer cells (Ben-Josef et al. J Urol 1999;161:970–6). It has also been demonstrated that subsets of prostate cancer express FSH receptor mRNA and protein at levels higher than those of normal and hyperplastic tissues (Mariani et al. J Urol 2006;175:2072–7) and that hormone-refractory prostate cancer cells express FSH and biologically active FSH receptor (Ben-Josef et al. J Urol 1999;161:970–6). This more profound and sustained reduction of FSH with degarelix could be a further alternative theory as to why it appears to be more effective

2. Additional analysis of the Secondary Endpoint of Biochemical Recurrence Rate in a Phase III trial (CS21) Comparing Degarelix 80mg Versus Leuprolide in Prostate Cancer Patients Segmented by Baseline Characteristics, (Tombal B et al. Eur Urol 2010.) showed that degarelix reduced PSA levels more rapidly than leuprorelin, irrespective of baseline disease stage and PSA progression-free survival was significantly longer with degarelix than leuprorelin in the ITT population. Also, patients with baseline PSA >20 ng/mL were significantly less likely to experience PSA failure with degarelix in an unadjusted analysis.

3. The CS21 a (Phase III Extension Trial with a 1-arm crossover from leuprolide to degarelix (Crawford E.D et al. J Urol 2011.) demonstrated that men switching from leuprorelin to degarelix, experienced a lower rate of PSA failure or death following an interim analysis at 27.5 months.

4. Data investigating the changes in serum alkaline phosphatase (s-ALP) levels in patients with prostate cancer receiving degarelix or leuprolide (Schroder F.H et al. BJU Int 2009) showed that greater S-ALP reductions were seen in patients with metastatic disease receiving degarelix compared with leuprorelin and that the late rises in S-ALP seen in leuprorelin patients (indicating possible therapy failure) were not observed in those receiving degarelix. These data suggest better S-ALP control and potentially longer control of skeletal metastases with degarelix.

Important data have previously been submitted to NICE with regards to cardiovascular (CV) morbidity and mortality. This is a major complication for men with prostate cancer being treated with LHRH agonists and represents a great clinical and economic burden. It is important to note that although the Albertson paper is a pooled analysis, all the original data from prospective studies has been independently assessed by Albertson's

team. The patients in both groups were evenly matched for disease state and previous co-morbid factors. Even though this is not a randomised, prospective study, there is a strong signal of a difference and there are patients with pre-existing CV risk who could benefit from degarelix over a LHRH agonist. The conclusions from this paper were that over one year of treatment, when patients with a history of CV disease at baseline were treated with degarelix, they had a significantly lower probability of a serious CV event or death than those treated with a LHRH agonist. There was also a reduction in risk of experiencing a serious CV event of greater than 50% compared with those treated with a LHRH agonist.

The rationale for the differences seen in cardiovascular events in men with a pre-existing cardiovascular disease are summarised below as in the Albertson paper. The hypotheses are that the adverse effects on CV disease of LHRH agonists could be the de-stabilisation of established vascular lesions. Most acute cardiovascular events, including myocardial infarction and stroke, are caused by rupture of an atherosclerotic plaque.

Activation of the GnRH receptors results in T cell activation including increased proliferation and expression of the IL-2 receptor degarelix as an antagonist would not have this effect. In addition GnRH antagonists suppress both LH and FSH as opposed to GnRH agonists which primarily suppress LH. FSH receptors have been found on the luminal endothelial surface of proliferating tissue and may also play a role in endothelial cell function, lipid metabolism and fat accumulation that may increase the risk of cardiovascular disease in men on LHRH agonists. These hypotheses are all supported by the observation that a GnRH antagonist is associated with a lower incidence of cardiac events only in subjects with pre-existing cardiovascular disease and that this difference becomes apparent within seven months.

In summary, we would propose that degarelix should be available as an option for:

- **men with high volume advanced (metastatic) disease who will benefit from immediate therapy with rapid reduction to testosterone and will avoid catastrophic consequences of any tumour flare eg spinal cord compression.**

Name	[redacted]
Organisation	
Role	NHS Professional
Job title	Consultant Urologist
Location	England
Conflict	No
Disclosure	
Comments	986 General I have been using degarelix since its introduction in 2009 and to change practice of a well established drug with evidence based effectiveness and specific clinical indications is not good medical practice. It's use in the acute management of metastatic prostate cancer particularly for symptomatic men with bone pain, spinal cord compression or ureteric instruction is well established. My practice has always to switch men after a month or so to conventional ADT to minimise costs for the NHS. I do not support the recommendation from NICE and I believe patient care will be severely compromised and I don't believe the costs to be excessive compared to many oncology drugs in common use.
Submission date	2015 06 21

Dear Helen,

Further to your request for clarification on our response to the latest Appraisal Consultation Document (ACD), please find the information requested set out below.

1. **Pricing Policy**

We are fully aware, as you know, of the requirement for any patient access schemes or pricing changes to be approved by the Department of Health (DH). Indeed, you and Meindert have been very helpful in discussing with us suggestions that might satisfy these requirements. However, you are also aware that, despite several calls with the Department, the provision of a rebate in primary care continues to prove problematic. As yet, we have been unable to secure a process that meets the requirements laid down by the DH.

We have therefore modelled all scenarios at full trade price, in line with the guide to the methods of technology appraisals.

Because of the issues that we face with the DH, and in response to your advice that contesting the ACD purely on clinical grounds would be unlikely to yield a positive outcome, our only option has been to reduce the trade price. As you are aware, there are corporate limitations as to the extent to which we can offer a lower price, and this is why we have also included an economic analysis at the lower price. Given that the model shows we are dominant at full trade price, the further reduction is indicative of our desire to find a mutually acceptable outcome in this appraisal.

One additional point; we DO have a Commercial Medicines Unit (CMU) approved tender price in secondary care that we have NOT included in the analysis. We will, however, continue to honour this price to hospitals purchasing directly from our wholesaler and will guarantee to continue to do so for the lifetime of the Institute's eventual guidance on this.

2. **A clinically derived and workable definition for the sub group suitable for this treatment**

You are correct in your interpretation that the Delphi Study supports the sub-groups for which we believe degarelix will offer distinct benefits.

One of the biggest issues that the Committee has faced throughout the process is how accurately to describe the intended sub-group, so that clinicians are clear about where to use the product and do not over use it to the detriment of NHS resources. In addition to the clinical community, the committee also concluded that degarelix offers a benefit over existing treatments where a rapid reduction of testosterone would be desirable (ACD, May 2015 §4.6). The Delphi panel study describes those sub-groups and validates that they are readily recognisable to the vast majority of clinicians. It is in these more urgent situations where the use of an agonist would require a delay of 7 – 10 days whilst an anti-androgen takes effect before the agonist can be administered. The sub-group, as defined and explained by clinical experts, represents circa 12 to 15% of all patients.

3. **A review of cost efficacy of antagonists over agonists in the sub group – taking into account the cost benefit of rapid symptom relief on hospital stay**

As stated within our draft response, the Committee acknowledges that Ferring was unable to submit cost-effectiveness analyses prior to the AC meeting within the subgroup of patients who would benefit from a rapid reduction in testosterone. As such we have provided cost utility analyses within the relevant subgroup. This is provided for two populations in line with the evidence collected via the Delphi consultation process:

- Patients who will benefit from a rapid reduction in testosterone
    - Painful bony metastases
    - High-volume bony metastases (≥4; with one outside the pelvic/spine region – based on the STAMPEDE/ CHAARTED trial definition)
    - Ureteric obstruction
    - High potential for spinal cord compression
- Patients with pre-existing cardiovascular disease

The existing cost-effectiveness model was substantially adapted to provide a simplified model focusing upon the benefits of degarelix in terms of rapid reduction in testosterone to address the relevant decision problem. All differences from the

original model are clearly stated within the response document provided and the analyses are based on the Committee's preferred assumptions as described in section 4.20 of the ACD issued on May 2015.

The only changes made beyond this relate to modifications to make the data relevant to this specific subgroup of patients, namely those that would benefit from a rapid reduction in testosterone. These changes are:

- An evaluation of the rate of SCC and the proportion of patients requiring treatment with degarelix, to capture that appropriate sub group
- updating the life expectancy of patients to reflect the subgroup
- the inclusion of the costs of hospital stay while awaiting treatment with anti-androgens (not a relevant concern in the overall advanced prostate cancer population but very relevant to this subgroup)
- an assessment of quality of life for patients with high volume disease from the CS21 clinical trial better to reflect the appropriate patient group – presented as scenario analysis only.

In accordance with the appeal decision, only benefits related to the group of patients at risk of spinal cord compression are included. Other groups of patients identified as likely to experience substantial benefit from rapid reduction in testosterone are:

- Patients with elevated ALP or abnormal LFTs (as anti-androgens can cause severe liver toxicities so flare cover is not possible)
- Patients with a CT scan showing blocked urethra / BOO (hydro-nephrosis or enlarged lymph nodes). These patients go into renal failure if testosterone is not brought down

The potential benefit of flare reduction in these patients is not included in this analysis.

In fact the original calculations can easily be traced to the original reference case model within the Excel file by simply un-hiding the relevant sheets. If there are any specific methods that are not clear within the documentation already provided, we are happy to clarify.

The time horizon specified within the simplified model for treatment is in line with clinical expert opinion of the life expectancy of patients presenting with high volume disease. The lack of accounting for differences in life expectancy in this subgroup, through use of the original reference case model based upon the entire population of patients with advanced prostate cancer, was a concern noted at the previous committee meeting which has therefore now been addressed.

Sensitivity analysis functionality has now been added to the simplified model (no other changes have been made) in order to allow probabilistic assessment of the uncertainty within the model.

The model is attached to this letter complete with probabilistic analysis functionality. Lower, upper bound and distributional information for new parameters can be found on the 'Probabilistic Analysis' sheet; all parameters previously contained within the model are sampled as previously within the Parameters sheet (now unhidden). Probabilistic analysis is presented in the PSA Summary sheet. Results are consistent with the deterministic base case presented, indicating a 100% probability of cost-effectiveness at a £20,000 per QALY threshold.

a. Cardiovascular (CV) sub-group inclusion

Ferring has included this sub-group as we believe that the full evidence supporting the issue of CV events in patients with prostate cancer has not been put before the Committee and as such is being interpreted incorrectly. This potential misinterpretation has featured throughout the process of appraisal for this drug. Additional data was disallowed at that stage and that is why we would kindly ask the Committee to consider the full picture now. This view is supported by an overwhelming number of clinicians via the Delphi study and we continue to believe that the full evidence supporting the issue of CV events in patients with prostate cancer has yet to be fully reviewed by the Committee. A potential misinterpretation of the CV data came to light in the appeal hearing and additional explanation presented at this stage may allow a more informed review.

Our response to the ACD submitted on the 26th June 2015 outlines the reasons and rationale, which has been reproduced below:

3 key assumptions underpin the Committee's current position on the CV benefit, namely:

- The increase in conventional cardiovascular risk factors was due to androgen deprivation (section 3 ACD May 2015) – changes in blood lipids, increased plasma insulin levels & increased risk of metabolic syndrome – hence there would be no difference between degarelix and an agonist as both lower testosterone to the same level
- The paper by Albertsen et al[8] was a pooled analysis and hypothesis generating only
- The belief that Albertsen results were driven mainly by the inclusion of one small study that showed a relative risk reduction of 80%, which was felt to be implausible.

We have sought to address these points below.

If the difference in CV events was purely driven by ADT then it would be reasonable to assume that an agonist would have the same effect as bilateral orchiectomy.

However, several large studies have highlighted a clear difference in associated risk of CHD, MI & sudden cardiac death in patients treated with LHRH agonists compared to orchiectomy (Keating 2006[9], Gandaglia 2010[10]). **It would be unreasonable therefore to conclude that increased CV risk is solely down to ADT**.

Furthermore, these data were not considered fully by the Committee in reaching its conclusion.

Agonists increase the risk of a thromboembolic event (MI etc) in the shorter term (Gandaglia[10]). There is no evidence, however, to suggest that antagonists increase that risk. Indeed the FDA published the following statement in October 2010:

"The U.S. Food and Drug Administration (FDA) has notified the manufacturers of the Gonadotropin-Releasing Hormone (GnRH) agonists of the need to add new safety information to the Warnings and Precautions *section of the drug labels. This new information warns about increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke) in men receiving these medications for the treatment of prostate cancer."*

Underlying risk is also driven by the presence of pre-existing CV disease. A plausible explanation of how antagonists avoid risk appears to have been misinterpreted by the Committee which refers to "degarelix's potential effect of reducing inflammation linked with atherosclerosis". **Degarelix does not claim to reduce inflammation or to be a secondary prevention therapy; it simply does not exacerbate the risk to the same extent as an agonist**.

Albertsen[8] results were presented both as the original pooled analysis and as a meta-analysis. In both analyses a statistical difference was observed between Degarelix and the agonist in terms of overall risk – favouring degarelix. By focussing solely on Albertsen[8], though, the Committee is ignoring the evidence referred to above, which demonstrates the negative impact that agonist therapy has on CV risk and that led to a warning being issued by the FDA[11].

The results of 3 key studies drive the overall result of Albertsen[8] and all favour degarelix. The 80% relative risk reduction observed in one of these may have been misinterpreted by the committee. If degarelix was considered to be cardioprotective then the 80% Relative Risk Reduction (RRR) would seem incredible given that statins only reduce relative risk by up to 40%[12]. **However, Degarelix is not cardioprotective and should not be interpreted as such. The apparent RRR is driven by the level to which the agonist increases risk and it is the significantly lower risk of degarelix that drives the relative reduction.**

Ferring acknowledges that over the longer term ADT does carry inherent risks for patients, however, it is the short term effect that has been clearly identified by several large studies that we would like to put before the Committee. It is for these reasons that we would kindly ask the Committee to re-assess this point.

I hope this fully answers your queries. We should, of course, be delighted to discuss any of the points above, if this is required.

Yours sincerely,

[redacted]

[redacted] – [redacted]/[redacted]
Ferring Pharmaceuticals Ltd

Discounted cost-effectiveness results, base case analysis

	Degarelix	**Triptorelin**	**Avg. LHRH**	**Degarelix vs triptorelin**	**Degarelix vs Avg. LHRH**
Probability of SCC	0.000	0.010	0.010	-0.010	-0.010
Drug costs	£4,029	£2,069	£1,742	£1,960	£2,288
Cost of SCCs	£0	£4,458	£4,458	-£4,458	-£4,458
Cost from increased hospital stay awaiting testosterone reduction	£0	£2,041	£2,041	-£2,041	-£2,041
Total cost	£4,029	£8,569	£8,241	-£4,539	-£4,212
QALYs	1.42	1.37	1.37	0.05	0.05
ICER				Dominant	Dominant

Scenario	**Cost of degarelix**	**Cost of triptorelin**	**QALYs with degarelix**	**QALYs with triptorelin**	**Incremental costs**	**Incremental QALYs**	**ICER**

Base case	£4,029	£8,569	1.42	1.37	-£4,539	0.05	Dominant
8% requiring treatment	£4,029	£10,798	1.42	1.34	-£6,769	0.08	Dominant
20% requiring treatment	£4,029	£6,785	1.42	1.39	-£2,756	0.03	Dominant
0.54% SCC rate for LHRH	£4,029	£6,618	1.42	1.39	-£2,589	0.03	Dominant
6.1% SCC rate for LHRH	£4,029	£32,439	1.42	1.08	-£28,410	0.35	Dominant
0.48% SCC rate for degarelix	£6,258	£8,569	1.40	1.37	-£2,310	0.03	Dominant
Equal rate of SCC in degarelix vs LHRH	£8,488	£8,569	1.37	1.37	-£81	0.00	Dominant
1 year life expectancy	£2,232	£5,681	0.72	0.70	-£3,448	0.03	Dominant
9 years life expectancy	£15,018	£26,219	5.70	5.49	-£11,201	0.22	Dominant
0 days increased hospitalisation with LHRH	£4,029	£6,528	1.42	1.37	-£2,498	0.05	Dominant
7 days increased hospitalisation with LHRH	£4,029	£9,385	1.42	1.37	-£5,356	0.05	Dominant
HRQL benefit with degarelix as per PSA>50 group	£4,029	£8,569	1.57	1.37	-£4,539	0.20	Dominant
HRQL benefit with degarelix as per metastatic group	£4,029	£8,569	1.47	1.33	-£4,539	0.14	Dominant

Contents

Delphi consultation summary

Methods

Scoping advisory board

- To inform the content of the Delphi consultation, an expert advisory board (n=6 advisors) was held. All advisors adhered to the following criteria:
    - Knowledge of the clinical trial data associated with degarelix and luteinising hormone-releasing hormone (LHRH) agonists
    - A healthcare professional with direct clinical responsibility for patients with advanced hormone-dependent prostate cancer (eg, consultant urologists or uro-oncology clinical nurse specialist).
- The advisors, as individuals and as a group, identified the specific patient populations that would be most suitable for treatment with degarelix. The rationale of this decision-making process – for example, on what evidence were their judgements made – was also discussed.
- The findings of the advisory board were then tested via a web-based Delphi consultation (described below).

Delphi consultation – participants

- Expert healthcare professionals were sourced from the delegate pool that attended the British Association of Urological Surgeons (BAUS) annual meeting in Manchester, either on Tuesday 16 June 2015 or Wednesday 17 June 2015.
- Participants completed ROUND 1 of the Delphi consultation using laptop stations at BAUS and during an evening meeting (provided and facilitated by Ferring Pharmaceuticals). Participants completed ROUND 2 of the Delphi consultation using personal computers, with a weblink provided via email (from 19 June to 23 June 2015).
- In addition to a briefing document that was provided in written and verbal format at the laptop stations, three screener questions were included within the Delphi consultation to ensure all participants had relevant experience in relation to the topic of the Delphi consultation.
- Delphi participants included the following specialities:
    - Urologist
    - Nurse specialist
    - Nurse practitioner
    - Medical oncology
    - Professor of men’s health.

Delphi consultation – questionnaire and consensus criteria

- Consensus was set at a pre-defined level of 'at least 70% of respondents in agreement' on a statement or question. Any statements or questions reaching consensus were removed between consultation rounds.
- In cases where there was disagreement, treatment statements and/or questions were reworded between rounds, with the aim of improving chances of agreement.
- Questions included a mixture of treatment statements and multiple-choice questions. Throughout the questionnaire, participants were asked to rate the appropriateness of each statement using the answer options provided, or to choose from a provided set of quantitative responses, depending upon the type of question.
- For all treatment statement questions, participants were given the opportunity to 'opt out' of providing an answer, as it was recognised that not every question may be fully applicable to each participant.
- For each treatment statement, participants had the opportunity to provide suggestions and/or comment using a free text box provided.

Results

Delphi consultation – ROUND 1

- ROUND 1 comprised of 29 questions.
- A total of 63 participants completed ROUND 1. After a review of the responses to the screener questions, two participants were excluded from the consultation and the results, as they stated they had no direct clinical responsibility for patients with advanced hormone-dependent prostate cancer being treated with either LHRH agonists or antagonists.
- Thus, the final dataset comprised of 61 participants:
    - N=54 (88.5%) were urologists
    - N=3 (4.9%) were nurse specialists
    - N=2 (3.3%) were nurse practitioners
    - N=2 (3.3%) were 'other' (medical oncology and professor of men's health).
- All participants (n=61/61; 100%) confirmed that they had direct clinical responsibility for patients with advanced hormone-dependent prostate cancer being treated with either LHRH agonists or antagonists.
- The majority of participants (n=57/61; 93.4%) described their own personal prescribing practices as either of the following:

- ‘I frequently prescribe degarelix for the treatment of advanced hormone-dependent prostate cancer’ (n=19)
- ‘I sometimes prescribe degarelix for the treatment of advanced hormone-dependent prostate cancer’ (n=38).

Statements achieving consensus at ROUND 1

The following treatment statements reached consensus after ROUND 1:

- **Statement 1: Degarelix should be considered as a treatment option for patients with advanced hormone-dependent prostate cancer. (Agree: n=59/61; 96.7% consensus)**

  Among the participants who agreed with the above statement, the rationale for agreement was based on:
  - Clinical trial evidence (n=53/59; 89.8%)
  - Personal experience (n=36/59; 61.0%)
  - Peer advice (n=23/59; 39.0%)
  - Hospital audit/real-world data (n=9/59; 15.3%)
  - Patient request (n=3/59; 5.1%).

- **Statement 2: Degarelix should be considered for patients presenting with symptomatic and/or high-volume metastatic, hormone-dependent prostate cancer with painful bony metastases. (Agree: n=60/61; 98.4% consensus)**

  Among the participants who agreed with the above statement, the rationale for agreement was based on:
  - Clinical trial evidence (n=48/60; 80.0%)
  - Personal experience (n=36/60; 60.0%)
  - Peer advice (n=28/60; 46.7%)
  - Hospital audit/real-world data (n=9/60; 15.0%)
  - Patient request (n=1/60; 1.7%).

- **Statement 3: Degarelix should be considered for patients presenting with symptomatic and/or high-volume metastatic, hormone-dependent prostate cancer with high-volume bony metastases (≥4; with one outside the pelvic/spine region – based on the STAMPEDE/ CHAARTED trial definition). (Agree: n=61/61; 100% consensus)**

Among the participants who agreed with the above statement, the rationale for agreement was based on:

- Clinical trial evidence (n=48/61; 78.7%)
- Personal experience (n=31/61; 50.8%)
- Peer advice (n=32/61; 52.5%)
- Hospital audit/real-world data (n=7/61; 11.5%)
- Patient request (n=1/61; 1.6%).

- **Statement 4: Degarelix should be considered for patients presenting with symptomatic and/or high-volume metastatic, hormone-dependent prostate cancer with ureteric obstruction. (Agree: n=50/61; 82.0% consensus)**

  Among the participants who agreed with the above statement, the rationale for agreement was based on:

  - Clinical trial evidence (n=25/50; 50.0%)
  - Personal experience (n=28/50; 56.0%)
  - Peer advice (n=24/50; 48.0%)
  - Hospital audit/real-world data (n=6/50; 12.0%)
  - Patient request (n=2/50; 4.0%).

- **Statement 5: Degarelix should be considered for patients presenting with symptomatic and/or high-volume metastatic, hormone-dependent prostate cancer with systemic signs of cancer; eg, weight loss, depression, anorexia, anaemia. (Agree: n=44/61; 72.1% consensus)**

  Among the participants who agreed with the above statement, the rationale for agreement was based on:

  - Clinical trial evidence (n=26/44; 59.1%)
  - Personal experience (n=27/44; 61.4%)
  - Peer advice (n=22/44; 50.0%)
  - Hospital audit/real-world data (n=8/44; 18.2%)
  - Patient request (n=1/44; 2.3%).

- **Statement 6: Degarelix should be considered for patients presenting with symptomatic and/or high-volume metastatic, hormone-dependent prostate cancer with high potential for spinal cord compression. (Agree: n=61/61; 100% consensus)**

  Among the participants who agreed with the above statement, the rationale for agreement was based on:

- Clinical trial evidence (n=41/61; 67.2%)
- Personal experience (n=36/61; 59.0%)
- Peer advice (n=31/61; 50.8%)
- Hospital audit/real-world data (n=12/61; 19.7%).

- **Statement 7: Degarelix should be considered for patients presenting with symptomatic and/or high-volume metastatic, hormone-dependent prostate cancer with pre-existing cardiovascular disease. (Agree: n=49/61; 80.3% consensus)**
  Among the participants who agreed with the above statement, the rationale for agreement was based on:
  - Clinical trial evidence (n=43/49; 87.8%)
  - Personal experience (n=17/49; 34.7%)
  - Peer advice (n=19/49; 38.8%)
  - Hospital audit/real-world data (n=9/49; 18.4%)
  - Patient request (n=1/49; 2.0%).

While not interrogated as formal treatment recommendation statements, but instead as part of panellists' own personal experience and/or known case studies, the following phrases reached consensus after ROUND 1:

- **Statement 8: In patients who are incapacitated and/or experiencing physical disability as a result of advanced hormone-dependent prostate cancer, treatment with degarelix can rapidly (<24 hours) reverse this disability, which is an outcome not provided by other available pharmacotherapy treatments. (Agree: n=43/61; 70.5% consensus)**

- **Statement 9: Treatment with degarelix provides rapid (<24 hours) relief of acute symptoms, which is an outcome not provided by other available pharmacotherapy treatments. (Agree: n=44/61; 72.1% consensus)**

- **Statement 10: LHRH antagonists are less cardiotoxic than LHRH agonists. (Agree: n=45/61; 73.8% consensus)**

- **Statement 11: LHRH antagonists provide a more rapid control of serum testosterone levels than LHRH agonists, and, therefore, should be considered as**

a treatment option to control the acute symptoms related to advanced, hormone-dependent prostate cancer. (Agree: n=56/61; 91.8% consensus)

Statements not achieving consensus at ROUND 1

The following treatment statements and questions failed to reach a consensus after ROUND 1. These statements were amended (using information from the free text responses provided by the panellists) for further consultation at ROUND 2.

- **Degarelix should be considered for patients presenting with symptomatic and/or high-volume metastatic, hormone-dependent prostate cancer with PSA [……..].**
    - When asked to define a PSA value to describe a patient population suitable for degarelix to be considered as a treatment option, respondents answered in the following fashion: ≥20 ng/ml (n=20; 32.8%); ≥40 ng/ml (n=12; 19.8%); ≥150 ng/ml (n=13; 21.3%); ≥200 ng/ml (n=4; 6.6%)
    - The statement was revised to: '*PSA levels alone are insufficient to guide treatment decisions for men with advanced, hormone-dependent prostate cancer'*, for consultation in ROUND 2.

- **To what extent do you agree with the positioning of degarelix by NICE, as a result of the current wording of the draft recommendations?**
    - Delphi participants responded in the following fashion: Agree (n=6; 9.8%); Neutral (n=10; 16.4%); Disagree (n=42; 68.9%)
    - This statement was revised to: '*The current NICE treatment recommendation for degarelix will have a negative impact on the treatment options available for patients with advanced, hormone-dependent prostate cancer'*, for consultation in ROUND 2.

- **Treatment with degarelix has allowed bed-bound patients to become mobile within less than 24 hours (eg, between evening and morning ward rounds), which is not provided by other available pharmacotherapy treatments.**
    - Delphi participants responded in the following fashion: Agree (n=30; 49.2%); Neutral (n=16; 26.2%); Disagree (n=3; 4.9%)
    - This statement was revised to: *'Treatment with degarelix has allowed bed-bound patients to become mobile within less than 72 hours, which is not*

provided by other available pharmacotherapy treatments', for consultation in ROUND 2.

- **Treatment with degarelix provides effective prevention of catastrophic complications of metastatic disease, which is not provided by other available pharmacotherapy treatments.**
    - Delphi participants responded in the following fashion: Agree (n=39; 63.9%); Neutral (n=14; 23.0%); Disagree (n=2; 3.3%)
    - This statement was revised to: '*Treatment with degarelix provides effective prevention of catastrophic complications of metastatic disease in patients presenting with a high symptom load, which is not provided by other available pharmacotherapy treatments'*, for consultation in ROUND 2.

Delphi consultation – ROUND 2

- ROUND 2 comprised of ten questions and was circulated to the panellists who completed ROUND 1 (n=61).
- A total of 29 participants responded to ROUND 2 (a 47% completion rate):
    - N=24 (82.8%) were urologists
    - N=2 (6.9%) were nurse specialists
    - N=1 (3.5%) was a nurse practitioner
    - N=1 (3.5%) was a medical oncologist
    - N=1 (3.5%) was a professor of men's health.
- All participants (n=29/29; 100%) confirmed that they had direct clinical responsibility for patients with advanced hormone-dependent prostate cancer being treated with either LHRH agonists or antagonists.
- The majority of participants (n=26/29; 89.7%) described their own personal prescribing practises as either of the following:
    - 'I frequently prescribe degarelix for the treatment of advanced hormone-dependent prostate cancer' (n=6)
    - 'I sometimes prescribe degarelix for the treatment of advanced hormone-dependent prostate cancer' (n=20).

Statements achieving consensus at ROUND 2

The following treatment statements reached consensus after ROUND 2.

- **Statement 1: PSA levels alone are insufficient to guide treatment decisions for men with advanced, hormone-dependent prostate cancer. (Agree: n=22/29; 75.9% consensus)**

- **Statement 2: The current NICE treatment recommendation for degarelix will have a negative impact on the treatment options available for patients with advanced, hormone-dependent prostate cancer. (Agree: n=26/29; 89.7% consensus)**

- **Statement 3: Treatment with degarelix provides effective prevention of catastrophic complications of metastatic disease in patients presenting with a high symptom load, which is not provided by other available pharmacotherapy treatments. (Agree: n=24/29; 82.8% consensus)**

- **Statement 4: LHRH antagonists are less likely to cause undesirable, cardio-related consequences than LHRH agonists. (Agree: n=24/29; 82.8% consensus)**

Statements not achieving consensus at ROUND 2

Only one statement failed to reach consensus after Round 2.

- **Treatment with degarelix has allowed bed-bound patients to become mobile within less than 72 hours, which is not provided by other available pharmacotherapy treatments**
    - Delphi participants responded in the following fashion: Agree (n=14; 48.3%); Neutral (n=8; 27.6%); Disagree (n=2; 6.9%)
    - This statement was not amended for further consultation.

Conclusions

A panel of expert healthcare professionals provided consensus that degarelix should be considered as a treatment option within its marketing authorisation; ie, for patients with advanced hormone-dependent prostate cancer (n=59/61; 96.7%). In addition to this overarching statement of consensus, the Delphi consultation identified the specific, in-label patient populations that are most applicable for treatment with degarelix. There was consensus that degarelix should be considered as a treatment option in the following patient populations; those with:

- Painful bony metastases (Agree: n=60/61; 98.4% consensus)

- High-volume bony metastases (≥4; with one outside the pelvic/spine region – based on the STAMPEDE/ CHAARTED trial definition) (Agree: n=61/61; 100% consensus)
- Ureteric obstruction (Agree: n=50/61; 82.0% consensus)
- Systemic signs of cancer; eg, weight loss, depression, anorexia, anaemia (Agree: n=44/61; 72.1% consensus)
- High potential for spinal cord compression (Agree: n=61/61; 100% consensus)
- Pre-existing cardiovascular disease. (Agree: n=49/61; 80.3% consensus).

When asked for the rationale for participants' agreement with the above patient populations, the most common justification quoted was '*clinical trial evidence'* for the painful bony metastases, high-volume bony metastases, high potential for spinal cord compression and pre-existing cardiovascular disease populations. The most common justification quoted was '*personal experience'* for the ureteric obstruction and systemic signs of cancer subgroups.

The consensus attained from the Delphi consultation combines to form an overarching treatment recommendation as follows:

Degarelix should be considered for patients presenting with symptomatic and/or high-volume metastatic, hormone-dependent prostate cancer with one or more of the following:

- **Painful bony metastases**
- **High-volume bony metastases (≥4; with one outside the pelvic/spine region – based on the STAMPEDE/ CHAARTED trial definition)**
- **Ureteric obstruction**
- **Systemic signs of cancer; eg, weight loss, depression, anorexia, anaemia**
- **High potential for spinal cord compression**
- **Pre-existing cardiovascular disease.**

The use of a PSA cut-off value within a treatment recommendation statement to describe a patient population suitable for treatment with degarelix was also consulted upon; however, Delphi panellists agreed that PSA levels alone are insufficient to guide treatment decisions for men with advanced, hormone-dependent prostate cancer. Thus, this result suggests the use of a PSA descriptor within future treatment recommendation statements is questionable.

This Delphi consultation process also investigated the potential outcomes of using degarelix in a real-world setting, when compared with LHRH agonists. The panel agreed that:

- In patients who are incapacitated and/or experiencing physical disability as a result of advanced hormone-dependent prostate cancer, treatment with degarelix can rapidly (<24 hours) reverse this disability, which is an outcome not provided by other available pharmacotherapy treatments. (Agree: n=43/61; 70.5% consensus)
- Treatment with degarelix provides rapid (<24 hours) relief of acute symptoms, which is an outcome not provided by other available pharmacotherapy treatments. (Agree: n=44/61; 72.1% consensus)
- Treatment with degarelix provides effective prevention of catastrophic complications of metastatic disease in patients presenting with a high symptom load, which is not provided by other available pharmacotherapy treatments. (Agree; n=24/29; 82.8% consensus)

Results from this Delphi consultation corroborated that degarelix, on the basis of its mechanism of action, provides clinically relevant outcomes when compared with LHRH agonists. Delphi panellists agreed that:

- LHRH antagonists are less cardiotoxic than LHRH agonists. (Agree: n=45/61; 73.8% consensus)
- LHRH antagonists are less likely to cause undesirable, cardio-related consequences than LHRH agonists. (Agree: n=24/29; 82.8% consensus)
- LHRH antagonists provide a more rapid control of serum testosterone levels than LHRH agonists and, therefore, should be considered as a treatment option to control the acute symptoms related to advanced, hormone-dependent prostate cancer. (Agree: n=56/61; 91.8% consensus)

When asked explicitly about the current NICE draft recommendations (as detailed within the appraisal consultation document 2 for degarelix), the Delphi panellists agreed that the current NICE treatment recommendation for degarelix will have a negative impact on the treatment options available for patients with advanced hormone-dependent prostate cancer. (Agree: n=26/29; 89.7% consensus)

Year	120mg units used	Actual Patients initiated	Actual Cumulative	**SMC predicted cumulative** at 11% mkt share	notes	
2011	>70	>35	35			
2012	115	58	93			
2013	151	76	169			
2014	266	133	302			
T1 2015	94	47	349			
T2/3 2015	(200)	(100)	549		Estimate based on T1 2015 actuals	
5 year data			**549**	**811**		

From: [redacted]

Sent: [redacted]

To: [redacted]

Subject: FW: CMU National Branded Framework Agreement for attachments

Importance: High

From: [redacted]

To: [redacted]

Sent: [redacted]

Subject: CMU National Branded Framework Agreement

Dear [redacted],

I have been asked to contact you on behalf of the CMU regarding Degralix.

I can confirm that this currently on a CMU Framework Agreement with Ferring as follows:

National Branded framework reference CM/PHR/13/5415/01.

1 May 2014 to 30 April 2016, with a possible 24 month extension period.

Price reviews are possible after the first 12 months, so okay now.

A final decision hasn't been made yet, but we will either extend this agreement to 30 April 2017 or retender for one year only to tie in with the expiry of the latest national branded tender.

Kind regards,

[redacted]

[redacted]

Commercial Medicines Unit (CMU)

Medicines Pharmacy & Industry (MPI), Department of Health

Rutland House, Runcorn, Cheshire. WA7 2ES

Email: [redacted]

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From: [redacted]

Sent: [redacted]

To: [redacted]

Subject: Independent testimonial regarding current rebate scheme for attachments

Importance: High

Ferring Pharmaceuticals has provided a Patient Access Scheme to the NHS in England for a number of years. This operates as a point-of-purchase discount ([redacted]) for Hospital Trust purchasers, and as a rebate paid to whichever is the relevant Primary Care Commissioning Organisation.

The PAS has operated without any apparent problems and has delivered substantial savings to the NHS in the North East during this time. The primary care rebate aspect is a necessity in order to ensure that there is sufficient product available to meet UK patient demand and to reduce the risk of counterfeit products entering the UK and other markets via the grey market. The rebate component has been maintained through several commissioner reorganisations and realignments within the North East and has remained flexible to commissioner demands, for example in respect of frequency of payments. In addition, it is relatively easy for Primary Care Commissioners to access accurate and timely usage data on which to claim the agreed rebate. In summary, the PAS which Ferring has provided for a number of years in relation to Degarelix has a proven track record of delivering the expected purchasing efficiencies.

About: [redacted] Spec Comm Team, NHS England.

[redacted]

Declaration: [redacted] has no financial interest or relationship, past, present or planned, with Ferring Pharmaceuticals, or any related patient or clinical interest group or any other related commercial party.

This statement has been voluntarily provided and no payment has been received. The views represented are [redacted]'s own and do not necessarily represent those of any employer, past or present.

<<<<<

[redacted]

NHS England

[redacted] Specialised Commissioning Team

[redacted]

Email: [redacted]

Office: [redacted]

ERG Base Case Model - pre existing CV disease (model 1)

Base Case

Treatment Arm	Totals			Incremental Costs	Incremental QALY Gained	Incremental Life Years Gained	Cost per QALY
	Costs	QALYs Gained	Life Years Gained				
Triptorelin 3 Monthly (Decapeptyl)	£17,333	4.049	6.856				
Degarelix	£31,462	5.412	9.549	£14,129	1.362	2.69	**£10,371**

10% Cost Discount

Treatment Arm	Totals			Incremental Costs	Incremental QALY Gained	Incremental Life Years Gained	Cost per QALY
	Costs	QALYs Gained	Life Years Gained				
Triptorelin 3 Monthly (Decapeptyl)	£17,333	4.049	6.856				
Degarelix	£30,215	5.412	9.549	£12,882	1.362	2.69	**£9,455**

15% Cost Discount

Treatment Arm	Totals			Incremental Costs	Incremental QALY Gained	Incremental Life Years Gained	Cost per QALY
	Costs	QALYs Gained	Life Years Gained				
Triptorelin 3 Monthly (Decapeptyl)	£17,333	4.049	6.856				
Degarelix	£29,592	5.412	9.549	£12,258	1.362	2.69	**£8,998**

Model 2

Basecase

	Degarelix	Triptorelin	Average LHRH	Degarelix vs Triptorelin	Degarelix vs Average LHRH
Probability of SCC	0.000	0.010	0.010	-0.010	-0.010
Drug costs	£3,131	£1,600	£1,742	£1,531	£1,390
Cost of SCCs	£0	£4,458	£4,458	-£4,458	-£4,458
Cost from increased hospital stay awaiting testosterone reduction	£0	£2,041	£2,041	-£2,041	-£2,041
Total cost	£3,131	£8,100	£8,241	-£4,968	-£5,110
QALYs	1.42	1.37	1.37	0.05	0.05
ICER				Dominant	Dominant

10% Discount

	Degarelix	Triptorelin	Average LHRH	Degarelix vs Triptorelin	Degarelix vs Average LHRH
Probability of SCC	0.000	0.010	0.010	-0.010	-0.010
Drug costs	£2,818	£1,600	£1,742	£1,218	£1,077
Cost of SCCs	£0	£4,458	£4,458	-£4,458	-£4,458
Cost from increased hospital stay awaiting testosterone reduction	£0	£2,041	£2,041	-£2,041	-£2,041
Total cost	£2,818	£8,100	£8,241	-£5,282	-£5,423
QALYs	1.42	1.37	1.37	0.05	0.05
ICER				Dominant	Dominant

15% Discount

	Degarelix	Triptorelin	Average LHRH	Degarelix vs Triptorelin	Degarelix vs Average LHRH
Probability of SCC	0.000	0.010	0.010	-0.010	-0.010
Drug costs	£2,662	£1,600	£1,742	£1,061	£920
Cost of SCCs	£0	£4,458	£4,458	-£4,458	-£4,458
Cost from increased hospital stay awaiting testosterone reduction	£0	£2,041	£2,041	-£2,041	-£2,041
Total cost	£2,662	£8,100	£8,241	-£5,438	-£5,579
QALYs	1.42	1.37	1.37	0.05	0.05

ICER	**Dominant**	**Dominant**

Degarelix for treating advanced hormone-dependent prostate cancer: ERG comments on ACD response submitted by Ferring

Sophie Whyte, Research Fellow, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA
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21st October 2015

Introduction

NICE released a second appraisal consultation document (ACD2)[1] on 5th June 2015. Following this Ferring submitted a response to the ACD2 on 26th June 2015. Following a request for clarification from NICE, additional information was submitted by Ferring in September 2015.

The additional evidence submitted by Ferring comprises:

(1) A Delphi study to identify a subgroup most suitable for treatment with degarelix.
(2) A description of other key differences between GnRH antagonists and LHRH agonists
(3) A new health economic assessment
(4) Analyses undertaken using discounted prices for degarelix.

Information received 26th June 2015:

- ACD response (15 page report)
- Appendix A – Delphi panel report (11 pages)
- Appendix B1 – Excel model
- Appendix B2 – Simpler excel model
- Appendix C - Scottish usage data table (1 page)
- Appendix D - CMU National Branded Framework Agreement (email)
- Appendix E – Testimonial for current rebate scheme (email)
- Appendix F – HE outputs at discounted rates (Excel sheet)
- Appendix G - QoL supporting data (4 files of Stata output and 1 reference)

Clarification July 2015:

- Letter from NICE to Gavin Gandy (Ferring)

Information received September 2015:

- Clarification on ACD response (3 pages)
- Excel model with PSA functionality
- Table of discounted cost effectiveness results (1 page)

The information submitted by Ferring in June and September 2015 will be hereafter referred to as the 'company's ACD response.'[2] This document provides a critique by the ERG of the company's ACD response. Where appropriate, we also refer to the original company submission (CS) for this STA dated August 2013[3] and the Evidence Review Group report on that submission.[4]

1. Delphi study to identify a subgroup most suitable for treatment with degarelix

The Delphi study was undertaken to validate the findings of an expert advisory board convened by Ferring. Sixty-one healthcare professionals with direct clinical responsibility for patients with advanced hormone-dependent prostate cancer being treated with LHRH agonists or antagonists took part in the first round. Participants in the Delphi process were delegates attending the annual meeting of the British Association of Urological Surgeons (BAUS). The vast majority (54/61) were urologists.

Participants reached a pre-defined level of consensus (at least 70% agreement) on 11 statements concerning the role of degarelix in the treatment of patients with advanced hormone-dependent prostate cancer. Four statements did not reach consensus in round one and were amended for discussion in the second round of the study. Twenty-nine participants (47%) completed the second round and reached consensus on a further four statements. Only one statement failed to achieve consensus after round 2 and this was not carried forward for further consultation.

Comments on Delphi study

There appear to be no standard criteria for assessing the quality of Delphi studies but a key aspect is the selection of an appropriate range of participants.[5,6] Participants need to be knowledgeable about the topic but also reasonably impartial. Bias can arise because people with a direct interest in the outcome are more likely to be willing to take part in the Delphi process, which can be time-consuming, especially if several rounds are involved.

In the case of this particular study, it appears that participants were self-selected, although the company specified criteria that they should meet. Almost all were currently prescribing degarelix and the sample included attendees at a meeting organised by Ferring. Thus, it appears likely that the participating clinicians were predisposed to favour the wider use of degarelix and this was reflected by the high degree of consensus achieved on many of the statements in the first round of the Delphi process.

Subgroups identified

The Delphi study identified a number of criteria for identifying patients considered suitable for treatment with degarelix. Whilst some of these were related to specific symptoms or clinical features, others were less clearly defined, in particular 'systemic signs of cancer' and 'high potential for spinal cord compression'. The difficulty of identifying patients with high potential for spinal cord compression among the larger group of patients with spinal metastases was discussed at some length in the second ACD[1] (Sections 4.11 and 4.12) and the company's ACD response[2] does not include any new evidence to clarify this issue. The reference to patients with 'systemic signs of cancer' appears to be new and the company has not provided any evidence to support the statement that this is a distinct

subgroup of patients who would benefit from treatment with degarelix. As with 'high potential for spinal cord compression', it would appear to be difficult to distinguish patients with 'systemic signs of cancer' from the overall population of patients with spinal metastases.

2. Efficacy of antagonists over agonists

This section of the company's ACD response[2] argues that the previous focus on the role of degarelix in reducing the risk of a 'testosterone flare' was misplaced and that the key benefit of degarelix is 'a rapid reduction in testosterone and other sex hormones' (page 2). The rapid action of degarelix is contrasted with a 7 to 10 day delay when an agonist is used because of the time required for anti-androgen treatment to take effect. The company's ACD response states that this delay leads to a 'possible increased risk of complications, a poorer quality of life, additional hospital bed occupancy and potential adverse consequences such as spinal cord compression and bladder outlet/ureteric obstruction' (page 2).[2] The ERG notes that no evidence is presented in the company's ACD response to substantiate the treatment delay associated with use of LHRH agonists or to support the claim of an increased risk of complications. This makes it difficult to assess the strength of the arguments presented.

3. New health economic assessment for the proposed subgroup

Proposed subgroup

The subgroup proposed in the company's ACD response was determined by the Delphi exercise and consists of patients requiring rapid testosterone reduction which is defined as follows:

> *"Degarelix should be considered for patients presenting with symptomatic and/or high-volume metastatic, hormone-dependent prostate cancer – characterised by any one of the following;*
>
> - *painful bony metastases*
> - *high-volume bony metastases (≥4; with one outside the pelvic/spine region – based on the STAMPEDE/ CHAARTED trial definition)*
> - *ureteric obstruction*
> - *systemic signs of cancer; eg, weight loss, depression, anorexia, anaemia*
> - *high potential for spinal cord compression*
> - *pre-existing cardiovascular disease"*
>
> (Company's ACD response,[2] page 1)

The ERG notes that the definition is vague in places e.g. systemic signs of cancer, high potential for spinal cord compression. This could result in degarelix being prescribed more widely than is clinically appropriate. Hence, there will be considerably uncertainty in the size of the subgroup. The company's ACD response uses a clinician estimated rate of 10% (range 8%-20%) for the proportion of metastatic

patients who 'require rapid testosterone reduction' to estimate the size of this proposed subgroup. However, within the model a rate of 12% has been applied in the base case. This estimate is not well supported in the company's ACD response. The following information was not provided: the number of clinicians providing estimates, the type of clinicians informing the estimate, or the confidence interval around the estimate. Hence there is uncertainty around the size of the subgroup for which treatment is proposed in the company's ACD response.[2]

The company's ACD response analysis sets out to model a subgroup of patients 'requiring rapid testosterone reduction'. It is implied that this is the same subgroup as defined by the Delphi although different language is used. The Delphi study uses the language 'degarelix should be considered for patients presenting with…'. The company's ACD response uses the language 'patients who require rapid testosterone suppression'. The ERG considers that it is unclear where the language 'who require' comes from. The subgroup includes patients with 'pre-existing CV disease' however these patients are included in a separate model. The subgroup modelled in the company's ACD response was not clear.

The modelling of benefits is restricted to the subgroup of patients who are at risk of spinal cord compression rather than representing the whole subgroup. The ERG suggests that this restriction will not cause the results to be biased towards degarelix because the model will be likely to result in an underestimate of benefits.

Reduced hospital stay

One key component of the new health economic model is the inclusion of the cost savings from reduced hospital stay due to rapid symptom relief. This component is a key driver of the model results. The modelling assumes that *'for patients initiating treatment in an inpatient setting degarelix,…. would be expected to save between 3 and 7 bed days in hospital'* (Company's ACD response, page 8)*;* this is based on clinical advice.[2]

Evidence in the original CS[3] (Section 7.5.5, page 171) states that degarelix and LHRH agonists may be administered in primary or secondary care. It is unclear if the expected reduction in hospital stay is appropriate if treatment is initiated in an outpatient setting. The model states that the assumption that 100% of patients are treated as inpatients is explored in sensitivity analyses but no such scenario analyses are presented in the results. The ERG has undertaken scenario analyses in which this parameter is varied (see Table 1).

In the company's ACD response, a reference to the second ACD[1] was provided for the 7 days hospitalisation; however, the ERG notes that this relates to the duration of bicalutamide treatment:

'*The clinical experts noted that, to reduce the risk of a testosterone flare, patients would usually have concomitant treatment with bicalutamide for at least 7 days before starting LHRH agonist therapy whereas testosterone suppression with degarelix would be expected to be immediate'* (ACD2,[1] page 49). Hence, the reference provided does not appear to provide supporting evidence.

The company's ACD response also states that the number of hospital bed days saved is based on clinical advice.[2] As no details were provided on: (i) how these clinicians were identified; (ii) the type of clinicians consulted, or; (iii) the number of clinicians consulted, the ERG believes this evidence to be associated with considerable uncertainty. The ERG comments that the expected number of additional bed days may in fact be dependent of the size of the subgroup benefitting from immediate testosterone reduction. For example, if the subgroup requiring treatment is smaller (with poorer prognosis) then the average number of additional bed days avoided may be greater.

Population

The proportion of newly diagnosed prostate cancer patients eligible for hormonal therapy is 39% in the original CS[3] (Section 2.2, page 17); however, a value of 24% is used in the company's ACD response model.[2] This difference will not impact on the cost per person or the ICER but is relevant for budget impact.

Cost of SCC

According to the original CS, the average cost of treating one person with SCC was £182,647. '*The total discounted cost associated with SCC is £1,836 in the original MS and the proportion of persons experiencing SCC adverse event was 1.02% hence the average discounted cost associated with treating one patient with SCC is £182,647*' (ERG report,[4] page 105). In the company's ACD response, the cost of treating SCC is dependent on life expectancy: £55,728 (2 years), £143,261 (6 years), £219,542 (10 years).[2]

Health-related quality of life and survival

The company ACD response[2] presents an analysis of health-related quality of life (HRQoL) for the subgroups: PSA>50 and metastatic disease. A statistically significant difference in HRQoL was found for the PSA>50 subgroup. A scenario analysis based on the values from the PSA>50 subgroup resulted in a significant difference in incremental QALYs. The ERG considers that it is unclear how the PSA>50 subgroup relates to the subgroup under consideration in the company's ACD response.

The mean survival for a prostate cancer patient following diagnosis of spinal metastases was assumed to be 2 years (evidence of 15-24 months). The ERG is unable to comment on whether the proposed

subgroup (who may not all have spinal metastases) would have better or worse survival than the subgroup of patients with spinal metastases.

Results presented within the company's ACD response

The company's ACD response[2] includes results for the newly defined subgroup based on the Delphi study. In the company's ACD response results from June 2015, discounted drug costs were applied. In the company's ACD response updated results from September 2015, list prices have been used for degarelix and the LHRH agonists. A range of scenario analyses were presented in the company's ACD response submission. In all of the scenarios presented, degarelix is cost saving compared to triptorelin for the subgroup of patients who would benefit from an immediate suppression of testosterone. The incremental costs were shown to be sensitive to the proportion of metastatic patients who would benefit from immediate testosterone suppression, life expectancy in the subgroup and the number of days increased hospitalisation.

The company's ACD response also includes results for the pre-existing CV disease subgroup based on the model from the original CS;[3] these are presented with a discount of 10% and 15% applied to degarelix prices. Values in this analysis were compared to those presented previously and were found to differ for both degarelix and the LHRH comparator for both costs and QALYs. Results previously presented for this subgroup are reported in the CS clarification response (see clarification response, question D3, Table 40). No details are provided by the company to explain how the model has been altered with respect to this subgroup.

Additional scenario analyses

The ERG presents some additional scenario analyses to supplement those presented within the company's ACD response including: (1) variation of the proportion of patients tested in an inpatient setting for additional hospital days; (2) variation in the size of the subgroup (as a proportion of all metastatic patients). The results are presented in Table 1 and show that if 0% of patients are treated as inpatients and the size of the subgroup is 40% of all metastatic patients then the ICER for degarelix may exceed £30,000 per QALY gained. This illustrates the importance of (i) having an accurate estimate of the size of the subgroup in which degarelix is recommended, and (ii) having robust data to inform the modelling of number of hospital days avoided.

Table 1: ERG additional scenario analyses

Scenario	Degarelix		Triptorelin		Incremental		
	QALYs	**Costs**	**QALYs**	**Costs**	**QALYs**	**Costs**	**ICER**
Company's base case	1.42	£4,029	1.37	£8,569	0.05	-£4,539	**Dominating**
50% treated as inpatients	1.42	£4,029	1.37	£7,548	0.05	-£3,519	**Dominating**
0% treated as inpatients	1.42	£4,029	1.37	£6,528	0.05	-£2,498	**Dominating**
Subgroup requiring treatment: 30% of metastatic patients	1.42	£4,029	1.4	£5,894	0.02	-£1,864	**Dominating**
Subgroup requiring treatment: 40% of metastatic patients	1.42	£4,029	1.41	£5,448	0.02	-£1,419	**Dominating**
0% treated as inpatients & Subgroup requiring treatment: 30% of metastatic patients	1.42	£4,029	1.4	£3,853	0.02	£177	**£8,128**
0% treated as inpatients & Subgroup requiring treatment: 40% of metastatic patients	1.42	£4,029	1.41	£3,407	0.02	£623	**£38,170**

4. Key points

The ERG notes the following key points:

- It appears likely that the clinicians participating in the Delphi exercise were predisposed to favour wider use of degarelix.
- The subgroup of patients suitable for treatment with degarelix resulting from the Delphi study includes a number of vague definitions, e.g. systemic signs of cancer.
- No evidence is presented in the company's ACD response to substantiate the treatment delay associated with use of LHRH agonists or to support the claim of an increased risk of complications.
- The evidence supporting the size of the subgroup proposed in the company's ACD response is associated with uncertainty.
- The evidence supporting the number of days of hospitalisation is not well described and hence associated with uncertainty.
- The subgroup modelled in the new economic analysis presented is unclear.

5. References

1. National Institute for Health and Care Excellence. Degarelix for the treatment of adult male patients with advanced hormone-dependent prostate cancer: Appraisal Consultation Document 2 (ACD2). NICE: London. 5th June 2015.
2. Ferring Pharmaceuticals. Company's response to Appraisal Consultation Document response. Degarelix for the treatment of adult male patients with advanced hormone-dependent prostate cancer. Ferring: Middlesex. September 2015.
3. Ferring Pharmaceuticals. Degarelix for the treatment of adult male patients with advanced hormone-dependent prostate cancer: Company's submission to NICE. Ferring: Middlesex. August 2013.
4. Uttley L, Whyte S, Gomersall T, Ren S, Wong R, Tappenden P, *et al*. Degarelix for the treatment of adult male patients with advanced hormone-dependent prostate cancer: Evidence Review Group Report. School of Health and Related Research: Sheffield. 2013.
5. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. *Journal of Advanced Nursing* 2000;32(4):1008–1015
6. Hsu C-C, Sandford BA. The Delphi technique: making sense of consensus. *Practical Assessment, Research & Evaluation* 2007;12(10):1–7.

Degarelix for treating advanced hormone-dependent prostate cancer: ERG comments on ACD response submitted by Ferring – erratum (additional ERG analyses including price discount)

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23rd October 2015

Table 1: ERG additional scenario analyses including 15% price discount for degarelix

Scenario	Degarelix		Triptorelin		Incremental		
	QALYs	**Costs**	**QALYs**	**Costs**	**QALYs**	**Costs**	**ICER**
Company's base case	1.42	£3,560	1.37	£8,569	0.05	-£5,009	**dominating**
50% treated as inpatients	1.42	£3,560	1.37	£7,548	0.05	-£3,988	**dominating**
0% treated as inpatients	1.42	£3,560	1.37	£6,528	0.05	-£2,968	**dominating**
Subgroup requiring treatment: 30% of metastatic patients	1.42	£3,560	1.40	£5,894	0.02	-£2,334	**dominating**
Subgroup requiring treatment: 40% of metastatic patients	1.42	£3,560	1.41	£5,448	0.02	-£1,888	**dominating**
0% treated as inpatients & Subgroup requiring treatment: 30% of metastatic patients	1.42	£3,560	1.40	£3,853	0.02	-£293	**dominating**
0% treated as inpatients & Subgroup requiring treatment: 40% of metastatic patients	1.42	£3,560	1.41	£3,407	0.02	£153	**£9,374**

Degarelix for treating advanced hormone-dependent prostate cancer

ERG addendum 3 November 2015
Sophie Whyte, ScHARR, University of Sheffield

The scenario analyses undertaken in the DSU report 'Degarelix for treating advanced hormone-dependent prostate cancer [id590] spinal cord compression associated with hormonal therapy in men with hormone-dependent metastatic prostate cancer: a systematic review and economic assessment' (April 2015) were repeated with a 15% discount.

This discount was applied to the cost of both the starter injections and the maintenance injection as follows:

Cost of Degarelix (Firmagon®)	**List price**	**Discounted price (15%)**
Degarelix starter injections	£260.00	£221.00
Degarelix maintenance injection	£129.37	£109.96

Table 6 [DSU report April 2015, p26]: Scenario analyses for different SCC rates relevant to subgroups

Population	Initial SCC event rate	ICER for degarelix vs. comparator		
		Triptorelin 3 monthly (decapeptyl)	Goserelin 3 monthly (zoladex)	Leuprorelin monthly (prostap)
No risk of SCC	0%	£342,984	£301,415	£291,399
Scope population: Locally advanced or metastatic	<0.96%	> £103,179	> £86,335	> £82,277
Metastatic Disease	0.96%	£103,179	£86,335	£82,277
Spinal metastases	>1.35%	< £71,387	< £57,821	< £54,552

Table 1: Scenario analyses for different SCC rates relevant to subgroups with 15% discount

Population	Initial SCC event rate	ICER for degarelix vs. comparator		
		Triptorelin 3 monthly (decapeptyl)	Goserelin 3 monthly (zoladex)	Leuprorelin monthly (prostap)
No risk of SCC	0%	£255,646	£214,077	£204,061
Scope population: Locally advanced or metastatic	<0.96%	> £67,790	> £50,946	> £46,888
Metastatic Disease	0.96%	£67,790	£50,946	£46,888
Spinal metastases	>1.35%	< £42,885	< £29,319	< £26,050

ERG addendum 10 November 2015, Sophie Whyte, University of Sheffield

This addendum presents results with a discount to degarelix of [redacted]% and [redacted]% applied. Discounting is applied to all doses of degarelix and to doses 3 onwards in different analyses. An analysis in which degarelix is compared to a weighted average of the different LHRH agonists is also presented. The ERG note that this weighted average is based on data from Table 6 of the company submission (p24). This Table uses IMS data from Ferring Pharmaceuticals from the period 2011-2012 and maybe subject to bias as several treatments are also used in additional indications outside advanced prostate cancer.

Proportions used for weighted average of comparators (from Company submission Table 6)	
Triptorelin 3 monthly (decapeptyl)	5%
Goserelin 3 monthly (zoladex)	41%
Leuprorelin monthly (prostap)	10%
Goserelin 1 monthly (zoladex)	18%
Leuprorelin 3-monthly (prostap)	25%
*Note formulations with market share <5% were excluded	

Table 1: [redacted]% discount applied to all degarelix doses: ICERs

Population	Initial SCC event rate	ICER for degarelix vs. comparator			
		Triptorelin 3 monthly (decapeptyl)	Goserelin 3 monthly (zoladex)	Leuprorelin monthly (prostap)	Weighted average of comparators
No risk of SCC	0%	£168,309	£126,739	£116,723	£137,856
Scope population: Locally advanced or metastatic	<0.96%	> £32,401	> £15,557	> £11,499	> £20,062
Metastatic Disease	0.96%	£32,401	£15,557	£11,499	£20,062
Spinal metastases	>1.35%	< £14,383	< £817	dominates	£4,445

Table 2: [redacted]% discount applied to all degarelix doses: ICERs

Population	Initial SCC event rate	ICER for degarelix vs. comparator			
		Triptorelin 3 monthly (decapeptyl)	Goserelin 3 monthly (zoladex)	Leuprorelin monthly (prostap)	Weighted average of comparators
No risk of SCC	0%	£156,664	£115,094	£105,078	£126,211
Scope population: Locally advanced or metastatic	<0.96%	> £27,682	> £10,839	> £6,780	> £15,343
Metastatic Disease	0.96%	£27,682	£10,839	£6,780	£15,343
Spinal metastases	>1.35%	< £10,583	dominates	dominates	£645

Table 3: [redacted]% discount applied to degarelix doses 3 onwards: ICERs

Population	Initial SCC event rate	ICER for degarelix vs. comparator			
		Triptorelin 3 monthly (decapeptyl)	Goserelin 3 monthly (zoladex)	Leuprorelin monthly (prostap)	Weighted average of comparators
No risk of SCC	0%	£171,926	£130,357	£120,341	£141,473
Scope population: Locally advanced or metastatic	<0.96%	> £33,867	> £17,023	> £12,964	> £21,527
Metastatic Disease	0.96%	£33,867	£17,023	£12,964	£21,527
Spinal metastases	>1.35%	< £15,563	< £1,998	dominates	£5,625

Table 4: [redacted]% discount applied to degarelix doses 3 onwards: ICERs

Population	Initial SCC event rate	ICER for degarelix vs. comparator			
		Triptorelin 3 monthly (decapeptyl)	Goserelin 3 monthly (zoladex)	Leuprorelin monthly (prostap)	Weighted average of comparators
No risk of SCC	0%	£160,522	£118,953	£108,937	£130,070
Scope population: Locally advanced or metastatic	<0.96%	> £29,246	> £12,402	> £8,344	> £16,907
Metastatic Disease	0.96%	£29,246	£12,402	£8,344	£16,907
Spinal metastases	>1.35%	< £11,842	dominates	dominates	£1,904

Table 5: [redacted]% discount applied to all degarelix doses: full breakdown of results

Removed due to commercial in confidence data

Table 6: [redacted]% discount applied to all degarelix doses: full breakdown of results

Removed due to commercial in confidence data

Table 7: [redacted]% discount applied to degarelix doses 3 onwards: full breakdown of results

Removed due to commercial in confidence data

Table 8: [redacted]% discount aaplied to degarelix doses 3 onwards: full breakdown of results

Removed due to commercial in confidence data