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30 April 2014

Dr Margaret Helliwell
Vice chair
National Institute for Health and Care Excellence
10 Spring Gardens
London SW1A 2BU

Dear Margaret

Re: Final Appraisal Determination – Appeal Against FAD - Degarelix for treating advanced hormone-dependent prostate cancer

On behalf of the British Uro-oncology Group we are hugely disappointed by the FAD: Degarelix for treating advanced hormone-dependent prostate cancer [ID590]**,** which suggests very restricted use of degarelix for men with advanced prostate cancer. The British Uro-oncology Group strongly appeals this FAD on Grounds 1a and 2:

Ground one: In making the assessment that preceded the recommendation, NICE has:

a) failed to act fairly

Ground two: The recommendation is unreasonable in the light of the evidence submitted to NICE.

Ground 1a: In making the assessment that preceded the recommendation, NICE has: failed to act fairly

1.1a. Change in wording from ACD to FAD without due consultation

We believe NICE has failed to act fairly by changing the wording from the ACD to the FAD without due consultation and this has significant implications on the potential use of the treatment.

In the ACD, it states:
Degarelix is recommended as an option for treating advanced hormone-dependent prostate cancer, only in people with spinal metastases who are at risk of impending spinal cord compression.

In the FAD this sentence appears as:

Degarelix is recommended as an option for treating advanced hormone-dependent prostate cancer, only in adults with spinal metastases who present with signs or symptoms of spinal cord compression.

This is a critical change:
The important advantage degarelix has over other Androgen Deprivation Therapies is the reduction in the risk of developing and/or exacerbating the acute complications of prostate cancer such as spinal cord compression. This means that the recommended use (WITH REGARD TO SPINAL CORD COMPRESSION) should be, as stated in both the ACD and FAD: that degarelix should be recommended as an option for men with high risk advanced prostate cancer **who are at risk of developing** spinal cord compression, **or who present with signs and symptoms** of spinal cord compression. Therapy aims to reduce complications. This is the opinion of those working in prostate cancer in order to achieve optimal therapy and minimal toxicity for men with advanced disease.

1.2a. NICE has been inconsistent in its acceptance and review of data in the context of other technology appraisals

NICE has failed to act fairly in its review of data submitted as part of the degarelix appraisal. NICE has not commented in this appraisal on pooled analyses or post hoc analyses (which included large numbers of men from prospective randomised studies). This is despite the fact that NICE has made recommendations on similar data methodologies as part of other appraisals in prostate cancer.

Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE

2.1 The FAD recommendation by NICE is unreasonable as it fails to accept data which shows demonstrable benefits for optimum patient care.

NICE has not commented in this appraisal on pooled analyses or post hoc analyses (which included large numbers of men from prospective randomised studies). This is despite the fact that NICE has made recommendations on similar data methodologies as part of other appraisals in prostate cancer.

We believe that degarelix should be recommended for:

- Men with high risk advanced prostate cancer who are at risk of developing spinal cord compression, or who present with signs and symptoms of spinal cord compression.
- Men with advanced (metastatic) prostate cancer who have been diagnosed with high risk disease (PSA >20) for initiation and maintainence
- Men with advanced (metastatic) prostate cancer presenting with a previous cardiovascular event.

We present again the data as outlined at the appraisal meeting and as our response to the ACD, given that in keeping with other appraisals in prostate cancer by NICE, data as part of pooled analyses or post hoc analyses (which included large numbers of men from prospective randomised studies) should be evaluated.

Comments previously submitted

We understand 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 I feel that we 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 was some discussion at the Appraisal Meeting regarding 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. This paper had apparently not been reviewed by the committee and should be considered before a final decision is made as it could be a further signal of efficacy*

Important data were submitted 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. The paper by Albertson had been made available and is to be published imminently. It is important to note that although this 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 for whom, in light of this data, I would be more comfortable prescribing degarelix than 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 destabilisation 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.

We do feel that these data cannot be ignored.

Conclusion

In conclusion, we would like to re-iterate our proposed recommendation for degarelix availability ie for:

- Men with high risk advanced prostate cancer who are at risk of developing spinal cord compression, or who present with signs and symptoms of spinal cord compression.
- Men with advanced (metastatic) prostate cancer who have been diagnosed with high risk disease (PSA >20) for initiation and maintainence
- Men with advanced (metastatic) prostate cancer presenting with a previous cardiovascular event.

We would obviously welcome our appeal being heard at a written or oral meeting.

Yours sincerely

[redacted]
Consultant Clinical Oncologist, University College London Hospitals
Chair and Trustee of British Uro-oncology Group

cc: [redacted]
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Treasurer and Trustee of British Uro-oncology Group