FROM DR HEATHER PAYNE, CONSULTANT CLINICAL ONCOLOGIST, UCL HOSPITALS AND CHAIR OF BRITISH URO-ONCOLOGY GROUP

Dear Kate

There are a number of comments to make which I would like to bring to the attention of the Appraisal Committee with regard to the clinical aspects and importance of the need for clinicians to have the choice of prescribing degarelix for men with advanced prostate cancer. Thank you in advance for sharing these with the Committee.

There is enthusiasm to have the opportunity to prescribe degarelix amongst oncologists and urologists who treat prostate cancer. The initial ACD decision is extremely disappointing for clinicians and patients who are suffering with advanced prostate cancer. I do agree that degarelix should be the treatment of choice for men with imminent spinal cord compression as a result of prostate cancer, but I (along with many of my colleagues) believe that this is not the only advantage and that there should be a wider indication for prescribing degarelix in routine practice.

I 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.

I do feel that these data cannot be ignored and as an Oncologist seeing over 800 new patients a year with prostate cancer, would feel it is difficult to now prescibe an agonist to men with previous cardivascular events knowing that there is an alternative that could reduce their chances of death from further cardiovascular events. This is also the opinion of many of my colleagues.

In summary:

I agree that degarelix should be the first therapy choice for men with risk of, or established, spinal cord compression, but feel very strongly that this should not be the only indication in view of the evidence described above.

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

- **men with advanced (metastaic) prostate cancer who have been diagnosed with high risk disease with a PSA >20 for initiation and maintainence**
- **also men with advanced (metatsatic) prostate cancer presenting with a previous cardiovascular event.**

Thank you again for your time and I would be grateful if you could confirm receipt of this email.

Kind regards

Heather Payne

[redacted]