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Degarelix for treating advanced hormone-dependent prostate cancer: An Evidence Review Group Perspective of a NICE Single Technology Appraisal

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Abstract

As part of its Single Technology Appraisal Process, the National Institute for Health and Care Excellence (NICE) invited the manufacturer of degarelix (Ferring Pharmaceuticals) to submit evidence for the clinical and cost-effectiveness of degarelix for the treatment of advanced hormone-dependent prostate cancer. The School of Health and Related Research Technology Appraisal Group at the University of Sheffield was commissioned to act as the independent Evidence Review Group (ERG). The ERG produced a critical review of the evidence contained within the company's submission to NICE. The evidence, which included a randomised controlled trial (RCT) of degarelix versus leuprorelin, found that degarelix was non-inferior to leuprorelin for reduction of testosterone levels and that degarelix achieved a more rapid suppression of prostate-specific antigen levels and subsequently decreased incidences of testosterone flare associated with LHRH agonists. However, protection against testosterone flare for the comparators in the clinical trials was not employed in line with UK clinical practice. Further claims surrounding overall survival, cardiovascular adverse events and clinical equivalence of the comparator drugs from six RCTs of degarelix should be regarded with caution due to flaws and inconsistencies in the pooling of trial data to draw conclusions. The cost-effectiveness evidence included a de novo economic model. Based on the ERG's preferred base case, the deterministic ICER for degarelix versus 3-monthly triptorelin was £14,798 per QALY gained. Additional scenario analyses undertaken by the ERG resulted in ICERs for degarelix versus 3-monthly triptorelin ranging from £17,067 to £35,589 per QALY gained. Subgroup analyses undertaken using the Appraisal Committee's preferred assumptions suggested that degarelix was not cost-effective for the subgroup with metastatic disease but could be cost-effective for the subgroup with spinal metastases. The company submitted further evidence to NICE following an initial negative Appraisal Committee

decision. Further analyses from the Decision Support Unit found that that whilst there was some evidence that degarelix could be cost-effective for a small subgroup of people with spinal cord compression (SCC), there were insufficient data on the potential size of this subgroup and the rate of SCC in order to estimate an ICER based on the evidence submitted by the company and a separately commissioned systematic review. NICE recommended 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.

Key points for decision makers

- Degarelix is non-inferior to leuprorelin in reducing testosterone to castrate level in those with all stages of prostate cancer requiring androgen deprivation therapy.
- Based on the assumptions used in the Evidence Review Group's (ERG) exploratory analyses, the incremental cost effectiveness ratios (ICER) for degarelix compared with triptorelin (administered every 3 months), goserelin (administered every 3 months) and leuprorelin (administered monthly) were at least £35,600, £28,000 and £26,200 per quality-adjusted life year (QALY) gained, respectively.
- Subgroup analyses undertaken using the Appraisal Committee's preferred assumptions suggested that degarelix was not cost-effective for the subgroup with metastatic disease and while degarelix could be cost-effective for the subgroup with spinal metastases, there were insufficient data on the size of this subgroup and the rate of spinal cord compression (SCC) to estimate an ICER.
- The National Institute for Health and Care Excellence (NICE) recommended 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 National Health Service (NHS) in June 2016.

1. INTRODUCTION

Health technologies must be shown to be clinically effective and to represent a cost-effective use of NHS resources to be recommended for use within the NHS in England. The National Institute for Health and Care Excellence (NICE) is an independent organisation responsible for providing national guidance on promoting good health and preventing and treating ill health in priority areas with significant impact. The NICE Single Technology Appraisal (STA) process usually covers new technologies soon after the UK market authorisation and is specifically designed for the appraisal of a single health technology within a single indication.[1] Within the STA process, the company provides NICE with a written submission, alongside a mathematical model, that summarises the company's estimates of the clinical effectiveness and cost-effectiveness of the technology. This submission is reviewed by an external academic organisation independent of NICE, the Evidence Review Group (ERG), which consults with clinical specialists and produces an ERG report. After consideration of the CS, the ERG report and testimony from experts and other stakeholders, the NICE Appraisal Committee formulates preliminary guidance in the form of an Appraisal Consultation Document (ACD), which indicates the committee's initial recommendations on the use of the technology. Stakeholders are subsequently invited to comment on the submitted evidence and the ACD, after which a subsequent ACD may be produced or a Final Appraisal

Determination (FAD) is issued, which is open to appeal. An ACD is not produced when the technology is recommended without restriction; in such instances, the FAD is produced directly.

This paper presents a summary of the ERG report[2] for the STA of degarelix for the treatment of advanced hormone-dependent prostate cancer, and the subsequent development of NICE guidance for the use of this drug in England. Full details of all relevant appraisal documents (including the appraisal scope, ERG report, company and consultee submissions, FAD and comments from consultees) can be found on the NICE website.[3]

2. THE DECISION PROBLEM

Prostate cancer is the most common cancer in men in the UK.[4] In 2014, the incidence of prostate cancer in England was 39,741 men and is highest in older men with the peak in absolute numbers between the ages of 65 and 84 years.[5] More than 10,000 prostate cancer related deaths occur each year in the UK. As well as age, other risk factors include black ethnic origin and a family history of prostate cancer in a close male relative.[5, 6] Prostate cancer may remain localised and develop slowly over many years from small tumours of cancer within the prostate gland. If the cancer spreads to tissues surrounding the prostate, such as the bladder and regional lymph nodes, the cancer is considered locally advanced. Prostate cancer is considered to be metastatic when it spreads beyond the prostate gland to other areas of the body such as the bones.[7]

Early, or localised, prostate cancer is unlikely to produce many symptoms. The symptoms of advanced prostate cancer occur when the prostate gland becomes enlarged and results in urinary tract problems and pain or blood when passing urine. Prostate-specific antigen (PSA) protein levels, which can be measured from blood samples, will be elevated in men with advanced prostate cancer compared with those with a healthy prostate.

2.1 Current treatment

Surgery, including prostatectomy or castration (orchidectomy) and/or radiotherapy may be offered to some men to treat early prostate cancer. However, androgen derivation therapy is the mainstay of treatment for men with advanced prostate cancer who are not eligible for surgery or who prefer the medical approach to castration than surgery. Androgen deprivation therapy, or androgen withdrawal, involves the use of a luteinising hormone releasing-hormone (LHRH) agonist drug or gonadotrophin-releasing-hormone (GnRH) antagonist drug to reduce the release of the luteinising hormone (LH) and follicle stimulating hormone (FSH) and subsequently the testosterone secreted by the testes to castrate levels. LHRH agonists used to treat prostate cancer include goserelin, leuprorelin, and triptorelin in combination with anti-androgen testosterone flare protection. Some prostate cancer is also managed using anti-androgen drug monotherapy.

Degarelix (Firmagon®) is a selective GnRH antagonist, which competitively and reversibly binds to pituitary GnRH receptors, leading to a rapid reduction in the release of the gonadotrophins LH and FSH. A decrease in LH and FSH levels results in a rapid reduction of testosterone secretion by the testes to castrate levels. Degarelix holds a European marketing authorisation for the treatment of adult male patients with advanced hormone-dependent prostate cancer. Degarelix is the first GnRH agonist to receive a licensed indication for the treatment of advanced

hormone-dependent prostate cancer in adult males in the UK. As a GnRH antagonist, it possesses a different mode of action to the LHRH agonist comparators which are also licensed for this indication.

In July 2013, NICE issued a final scope to appraise the clinical effectiveness and cost-effectiveness of degarelix, within its licensed indication, for the treatment of locally advanced hormone-dependent prostate cancer in men. In August 2013, the company (Ferring Pharmaceuticals) provided a submission to NICE relating to the clinical effectiveness and cost-effectiveness of degarelix for the treatment of locally advanced hormone-dependent prostate cancer in men.

3. THE INDEPENDENT EVIDENCE GROUP (ERG) REVIEW

The ERG report comprised a critical review of the clinical and cost-effectiveness evidence presented in the CS, which assessed the appropriateness of the company's analysis and interpretation of the evidence. The ERG had the opportunity to seek clarification on specific points in the CS, which resulted in the company providing additional information. The ERG also modified the company's decision analytic model to examine the impact of altering some of the key assumptions.

3.1 Clinical evidence provided by the company

The clinical effectiveness evidence in the company's submission (CS) was based predominantly on six randomised controlled trials (RCTs): two trials of degarelix versus leuprorelin (CS21[8] and CS37) and four trials of degarelix versus goserelin (CS28[9], CS30[10], CS31[11] & CS35), ranging in duration from 3 to 14 months. Four of the trials used the licensed dose of degarelix (240mg followed by monthly maintenance doses of 80mg); whilst two trials used unlicensed 3- or 6-monthly dose schedules, which limits the relevance of these two trials to the decision problem. The sample size in the RCTs ranged from 42 to 859 patients. The main pivotal trial of degarelix (CS21) had a primary endpoint of probability of testosterone levels ≤0.5ng/ml from Day 28 to Day 84. Pooled analyses using different combinations of the 6 RCTs were presented for: testosterone response; PSA progression-free survival (PFS); serum alkaline phosphosphatase, and; adverse events (AEs). The CS included pairwise meta-analyses performed for the following outcomes: reduction in prostate size; change in international prostate symptom score (IPSS); PSA change from baseline, and; overall survival (OS). The company conducted a network meta-analysis (NMA) for degarelix, goserelin, leuprorelin, triptorelin, and bicalutamide. The CS stated that due to lack of usable data on other outcomes, the NMA was restricted only to the outcome of OS.

Trial CS21 showed that degarelix (240mg/80mg) is non-inferior to monthly leuprorelin (7.5mg) for the primary endpoint of probability of testosterone levels ≤0.5 ng/ml from Day 28 to Day 364. Additionally, degarelix achieved a more rapid suppression of PSA levels (median reduction at Day 28) than leuprorelin ($p<0.0001$) in Trial CS21 which decreases the incidence of testosterone flare which is associated with LHRH agonists. The pairwise meta-analysis of mortality favoured degarelix however, the result only became statistically significant ($p=0.045$) when results from the CS35 trial, which used an unlicensed 3-monthly dose of degarelix, were included. No statistically significant differences were found for OS in the NMA, however, the forest plot showed that leuprorelin and goserelin were associated with increased mortality compared with degarelix, whilst mortality for triptorelin appeared to be lower than degarelix.

3.1.1 Critique of clinical evidence and interpretation

The ERG considered the included trials to be generally of good methodological quality. However, the ERG considered that the two trials which used unlicensed doses of degarelix were not fully applicable to the decision problem.

The target population was adult men with advanced hormone-dependent prostate cancer which includes both locally advanced and metastatic disease. The study populations for the included trials generally had lower PSA levels and consequently less advanced cancer than the licensed population expected in clinical practice in England. The pivotal trial CS21 was powered to show non-inferiority for the primary endpoint of reduction of testosterone to castrate level in those with all stages of prostate cancer requiring ADT. The trial was not powered to make substantive conclusions about the target population as the trial population included patients with other classifications including 'localised' and 'not classifiable' prostate cancer. The number of patients in Trial CS21 who were reported to have locally advanced or metastatic disease and would be considered relevant to the decision problem was 303 out of 607 patients (49% of the trial population). However, clinical advice sought by the ERG from three consultant urologists practicing across the UK suggested that this would have limited effect on the assessment of efficacy given that severity was balanced between the intervention and control arms across trials.

The NICE scope specified that the comparator LHRH agonists should be used in combination with short-term anti-androgen treatment (such as bicalutamide or cyproterone acetate) to prevent testosterone flare associated in the early stages of treatment with LHRH agonists. Testosterone flare protection was inconsistently used for patients in the comparator arms, with two trials providing flare protection at a much lower level than would be expected in current clinical practice in England.

The NICE scope specified bicalutamide monotherapy as a relevant comparator to degarelix. The CS excluded bicalutamide monotherapy on the basis of insufficient evidence to inform a robust NMA. Clinical advice received by the ERG suggested that whilst bicalutamide monotherapy may be a preferred treatment option in some patients, particularly those with locally advanced disease and for younger patients in whom maintenance of sexual function is preferable, it is used in a relatively small proportion of patients.

The CS contained simple pooled analyses of selections of the different trials for testosterone response; PSA PFS; serum alkaline phosphatase, and; AEs. The ERG noted that these should be interpreted with caution as data were not formally meta-analysed and simple pooling assumes that there is no difference between individual studies which may yield counterintuitive or spurious results. The company presented a post hoc pooled analysis of cardiovascular serious adverse events (SAEs) from the 6 included trials; these indicated that men with a history of cardiovascular disease (CVD) experienced a significantly lower risk of CVD AEs if treated with degarelix compared with an LHRH agonist. However, CVD SAEs were not a pre-defined clinical endpoint but were instead AEs which were collected post hoc and no effect has been demonstrated in men without pre-existing CVD. Clinical advice received by the ERG suggests that currently the evidence for a link between LHRH agonists and CVD is correlative and there is a lack of prospective evidence to base conclusions about a potential relationship

between these treatments and the cardiovascular risk. The ERG noted that the company attempted to assign causal conclusions without direct evidence to corroborate the assumptions.

The results of the company's meta-analyses should also be interpreted with caution. On the basis of the NMA, together with a paper[12] and poster[13] which do not include one of the comparators (triptorelin), the company assumed that the efficacy and safety profiles of the LHRH agonist comparators were equivalent. The ERG considered the assumption that the LHRH agonists: goserelin; leuprorelin and triptorelin are clinically equivalent to be unproven and therefore inappropriate. The International Prostate Symptom Score (I-PSS) questionnaire and prostate size outcomes only compared degarelix against goserelin and therefore the conclusion stated by the company about degarelix versus LHRH agonists is too broad. Similarly, the company's meta-analyses of OS and PSA response only compare degarelix against leuprorelin or goserelin and therefore conclusions about all LHRH agonists cannot be drawn.

The NMA used data from trials which were too short in duration to make meaningful conclusions about OS in this population. The absolute number of deaths in the included trials was small (41 out of 2,328 patients) and clinical advice received by the ERG suggested that comparative data relating to one-year survival should be treated with caution and that trials of this size and duration are not sufficient to capture meaningful differences in survival in this stage of disease. Clinical advice also suggested that at least 5-year follow-up would be required to gather appropriate numbers of events (deaths).

The CS presented a meta-analysis of AEs from the four RCTs (CS21; CS28; CS30; CS31) and concluded that overall, no statistically significant difference in the proportion of patients experiencing any AEs, death or SAEs was observed between the degarelix 240mg/80mg group and the LHRH agonist group. The ERG considered the frequency and nature of AEs for degarelix reported in the CS to be similar to levels seen in trials of goserelin, leuprorelin and triptorelin. Common long-term AEs included: impact on bone health; lower metabolism; cardiovascular risk; sexual dysfunction; gynecomastia; reduction in penile and testicular size; fatigue; hot flashes; anaemia, and; potential cognitive decline.

3.2 Cost-effectiveness evidence provided by the company

The CS presented a systematic review of cost-effectiveness studies which included three relevant studies. The review concluded that the studies were inadequate to fully inform decision-making in the UK context, hence a de novo model was required. The CS included a de novo Markov treatment-sequence model to estimate the costs and benefits of degarelix versus 10.8mg goserelin (Zoladex®) for patients with advanced hormone-dependent prostate cancer from the perspective of the NHS and Personal Social Services (PSS) over a 30-year (lifetime) horizon. Costs and health outcomes were discounted at a rate of 3.5% per annum. Scenario analyses included comparisons of degarelix versus goserelin (Novgos®) and triptorelin (Gonapeptyl®).

The company's model assumes that all patients receive each of the following treatment lines if still alive: first-line treatment with degarelix/LHRH agonists; anti-androgen addition; anti-androgen withdrawal; chemotherapy; abiraterone; supportive care, and; palliative care. The model also assumes that the health-related quality of life

(HRQoL) associated with each disease state either falls or remains constant as patients progress along the sequence. The model uses HRQoL data available from Trial CS21 which were mapped to the EQ-5D (3-level). The model includes the costs of drug acquisition, drug administration and monitoring costs for each treatment in the pathway. The model considered the impact of the following AEs on costs, HRQoL and mortality: fractures; joint-related signs and symptoms; cardiovascular events, and; spinal cord compression (SCC) Costs were based on NHS Reference Costs for 2011/2012 and personal social services research unit (PSSRU) costs which were validated by UK clinicians.

Transitions from first-line treatment were based on data for PSA progression with degarelix and LHRH agonists. The model assumes that each of the LHRH agonists (goserelin, leuprorelin and triptorelin) have equivalent efficacy. The model uses data from the CS21 and CS21A trials which compared degarelix to leuprorelin for a period of one year before crossover to degarelix was allowed for all patients. A hazard ratio (HR) for PSA progression of 1.71 (1.74) for leuprorelin compared with degarelix for the intention-to-treat (ITT) population (PSA>20ng/ml population) was estimated from the CS21 and CS21A trial data. PSA progression for degarelix was modelled using a log normal distribution. The HRs were applied to the parametric curves assuming proportional hazards. Two scenario analyses were also presented: (1) a scenario in which the efficacy of degarelix and LHRH agonists were assumed to be equal, and; (2) a scenario in which the efficacy of degarelix and LHRH agonists were assumed to be equal after 1 year.

Duration of response to subsequent lines of treatment was based on estimated response durations reported in the European Association of Urology (EAU) guidelines.[14] Mortality rates which were age specific and dependent on the presence of metastatic disease were derived from data from the Office for National Statistics (ONS)[15] and Scottish prostate cancer mortality data. Mortality for patients receiving first-line treatment was calculated based on the proportions of patients with localised, locally advanced and metastatic disease from Trial CS21. Patients receiving chemotherapy, abiraterone or supportive/palliative care were assumed to have metastatic disease so the model applied a metastatic disease mortality rate for these patients. However, a different mortality rate was applied for patients receiving abiraterone. An increased hazard of mortality was applied for patients with metastatic disease once they had progressed from first-line treatment.

The company's base case comparison of degarelix versus goserelin (3-monthly) suggested that degarelix produces cost savings of £1,697 per patient and a QALY gain of 0.58, hence degarelix was expected to dominate goserelin. The estimated cost savings were due to a reduction in subsequent-line therapies and cardiovascular/musculoskeletal events compared with LHRH agonists. A subgroup analysis for patients with PSA>20ng/ml resulted in cost savings of £1,691 and a QALY gain of 0.45 per patient for degarelix versus goserelin (3-monthly). A subgroup analysis for patients with baseline cardiovascular disease resulted in incremental costs of £6,856, incremental QALYs of 1.63 and an ICER of £4,216 per QALY gained for degarelix versus goserelin (3-monthly).

The CS presented a series of sensitivity analyses to test structural assumptions. The following assumptions had the greatest impact on the ICER: (a) if the efficacy of degarelix and LHRH agonists was assumed to be equal, the ICER for degarelix versus goserelin (3-monthly) was estimated to be £12,987 per QALY gained; (b) if the HR

for differential efficacy between degarelix and LHRH agonists was applied for one year (the duration for which there is comparative trial data), the ICER for degarelix versus goserelin (3-monthly) was estimated to be £3,751 per QALY gained; (c) if musculoskeletal AEs were excluded from the model, the ICER for degarelix versus goserelin (3-monthly) was estimated to be £2,484 per QALY gained, and; (d) if abiraterone was excluded from the model, the ICER for degarelix versus goserelin (3-monthly) was estimated to be £2,072 per QALY gained.

3.2.1 Critique of the cost-effectiveness evidence and interpretation

The ERG considered the CS to be complete with regard to relevant published cost-effectiveness studies. The ERG considered that the company's model adequately addressed the NICE Reference Case but noted that the economic evaluation had several significant limitations and that the CS did not contain an unbiased estimate of the technology's ICER. The limitations with the ICER estimates in relation to relevant populations, interventions, comparators and outcomes are discussed in turn below.

Clinical advice received by the ERG suggested that there is variation in the treatment sequence between patients, so the 'treatment sequence' model structure used was inappropriate. The ERG considered that a model structure that explicitly modelled time to metastatic disease and time to death and allowed variation in treatment sequences would be more appropriate, flexible and transparent. The ERG noted that the company's assumption that treatment with degarelix or LHRH agonists would stop at the point when chemotherapy is initiated did not universally reflect clinical practice and thus should not be used as a base case assumption. The ERG also considered that despite the paucity of evidence, subgroups could have been considered in exploratory analyses. For example, clinical advice suggested that there may be considerable additional benefit in avoiding flare and associated AEs in the subgroups of 'patients with spinal metastases with impending or actual spinal cord compression' and 'patients with high tumour volume with impending or actual urinary outflow obstruction.'

The ERG considered that the company's model should have included all relevant trial data rather than relying on one single trial, CS21. The ERG considered that the company's scenario analyses around efficacy assumptions were appropriate and useful. The ERG also considered that the uncertainty surrounding HRQoL values was adequately represented by the scenario analyses included within the CS. The costs used within the economic model were clearly described with the exception of the costs of treating SCC which were not well reported.

The company's sensitivity analyses addressed many of the key areas of structural uncertainty within the model. The model used to undertake the company's probabilistic sensitivity analysis was not provided by the company as part of the original submission or the company's clarification response and thus could not be verified by the ERG. The model validation undertaken by the company was not comprehensive. In particular, the health professionals who were consulted by the company did not review the viability of the extrapolation of AE data beyond the observed period within the clinical trial.

3.3 Additional work undertaken by the ERG

The ERG undertook a revised NMA using informative priors for the heterogeneity parameter and the baseline treatment effect, but non-informative priors for the treatment effects. The analyses showed that triptorelin was associated with lower mortality than leuprorelin (odds ratio [OR] 0.28; 95% credibility interval [CrI]: 0.06, 0.97). The ERG undertook an additional analysis taking into account the different study durations between the trials. These results were also in line with the OR results from the ERG's NMA.

The ERG undertook additional analyses including an ERG base case analysis applying the following assumptions: (i) 3-monthly triptorelin was included as a comparator; (ii) LHRH agonists treatment was assumed to be continued until death; (iii) the HR for differential efficacy was applied for one year; (iv) 70% of patients were assumed to receive chemotherapy after PSA progression, and; (v) the proportion of patients receiving abiraterone was assumed to be 70%. The ERG's base case suggested that compared with 3-monthly triptorelin, degarelix is associated with an additional cost of £3,659 and produces an incremental QALY gain of 0.25: the corresponding ICER for degarelix versus 3-monthly triptorelin was estimated to be £14,798 per QALY gained.

The ERG's scenario analyses demonstrated that this ICER was very sensitive to four model assumptions: (i) the exclusion of SCC AEs from the analysis; (ii) the modelling of fracture rates; (iii) the assumption that PSA progression affects mortality rates in metastatic patients, and; (iv) the assumption of equal efficacy for degarelix and LHRH agonists. The ICERs for degarelix versus 3-monthly triptorelin obtained were £25,486 per QALY when SCC AEs were excluded from the analysis; £21,950 per QALY when fracture rates were assumed to be the same for both arms; £17,067 per QALY when no increased risk of mortality due to PSA progression was applied; and £35,589 per QALY when the efficacy of degarelix and LHRH-agonists was assumed to be equal. Finally, an ERG scenario analysis which explored the possible benefits of degarelix for the subgroup of 'patients with spinal metastases with actual or impending SCC' suggested that degarelix had the potential to be cost-saving.

3.4 Conclusions of the ERG report

The decision problem addressed in the CS was relevant to the final NICE scope, however, the study populations were not fully reflective of the target population which related to men with advanced, hormone-dependent prostate cancer. In addition, the frequency of flare protection was considerably lower in the trials than would be expected in clinical practice in England.

The key areas of uncertainty included the following:

(a) The duration of the trials was inappropriate to determine OS benefits and the data supporting the relationship between PSA progression and OS with degarelix were inconclusive.
(b) LHRH agonists were considered to be equivalent in terms of efficacy and AEs without adequate justification. Efficacy and AEs for each LHRH agonist should have been modelled individually.
(c) The claim of reduced cardiovascular AEs for degarelix compared to LHRH agonists was based on selective pooling of trial data. The analysis should have compared the fit of additional parametric curves and the fit of the Weibull which was used in the CS was poor for some AEs.
(d) The data on PSA progression and AEs were for a maximum of one-year in duration so the company's model is based on extrapolation of these data which introduces considerable uncertainty.

4. NICE GUIDANCE

This section discusses some of the key issues considered by the AC in conjunction with advice from clinical experts and patient representatives. The full list of issues can be found in the FAD.[16]

4.1 Efficacy of degarelix

The Committee noted that degarelix was non-inferior to LHRH agonists in suppressing testosterone levels and acknowledged that it is particularly beneficial for avoiding testosterone flare. The Committee heard from the clinical specialists and patient experts that degarelix was particularly beneficial for people with spinal metastases who are at risk of impending SCC. It also heard from the clinical specialists that not all patients with metastases are at risk of having SCC and the proportion of patients at risk is small. The Committee acknowledged that although the proportion of patients at risk could be small, SCC is a serious and complex AE.

4.2 Uncertainties in the evidence

The Committee considered that the results for PSA progression and long-term PSA progression benefit for degarelix compared with LHRH agonists were highly uncertain and therefore no PSA progression benefit from degarelix compared with LHRH agonists could be assumed. The Committee also concluded that whilst it was plausible to assume equivalent clinical efficacy between LHRH agonists, there was a lack of robust evidence to support an OS benefit for degarelix compared with LHRH agonists. Additionally, the Committee noted that because of the uncertainty around the company's pooled analyses, the data were not sufficiently robust to confirm that degarelix would reduce the risk of cardiovascular events in people with pre-existing CVD compared with LHRH agonists.

The Committee noted that the company did not present any data on SCC because it did not occur in the included trials. The Committee acknowledged that there was a known relationship between testosterone suppression, no risk of surge and flare and prevention of SCC. Therefore, it concluded that degarelix may offer potential benefit compared with LHRH agonists for people with spinal metastases who are at risk of impending SCC.

The Committee discussed the cost-effectiveness results produced using the company's model. It noted that the results were based on a deterministic estimate of the ICER and that the company did not provide a probabilistic estimate of the ICER. The Committee noted that in the company's base-case analysis, degarelix dominated goserelin. It noted that these results were based on assumptions of greater clinical efficacy in terms of PSA progression, OS, and reductions in rates of fracture and of cardiovascular events for degarelix compared with LHRH agonists. It noted its earlier conclusions that the evidence informing these assumptions was considered to be subject to a high degree of uncertainty. The Committee concluded that the company's base case ICER was based on assumptions that were not plausible and was likely to overestimate the cost-effectiveness of degarelix compared with LHRH agonists.

The Committee noted that, based on the assumptions used in the ERG's exploratory analyses, the ICERs for degarelix versus LHRH agonists were at least £35,600 per QALY gained compared with triptorelin (administered

every 3 months), £28,000 per QALY gained compared with goserelin (administered every 3 months) and £26,200 per QALY gained compared with leuprorelin (administered monthly). It noted that the ICER for degarelix versus triptorelin was £103,200 per QALY gained when its preferred assumption of no differences in the rates of fractures and cardiovascular AEs between degarelix and the LHRH agonists was applied. The Committee noted that all ICERs were outside the range normally considered as a cost-effective use of NHS resources and concluded that degarelix could not be recommended for treating advanced hormone-dependent prostate cancer compared with LHRH agonists.

The Committee considered the ERG's exploratory analyses for people with spinal metastases with actual or impending SCC, which assumed that people receiving degarelix would not have SCC and that the efficacy of degarelix and LHRH agonists in terms of PSA progression and OS was equivalent. The Committee was persuaded, based on the ERG's analyses, that if the rate of SCC in this subgroup was higher than 3.5%, degarelix could dominate triptorelin. If the rate of SCC was lower than 3.5%, degarelix could still be cost-effective compared with triptorelin. On balance, the Committee concluded that based on comments from the clinical specialists and patient experts, who noted that degarelix provided an important benefit for people with spinal metastases who are at risk of impending SCC for which there are no treatments available, and the ERG's exploratory analysis, degarelix was a cost-effective use of NHS resources and could be recommended as an option for treating advanced hormone-dependent prostate cancer only for people with spinal metastases who are at risk of impending SCC.

4.3 Outcome of the Appraisal Committee meeting

In November 2013, based on the evidence available (including verbal testimony of invited clinical experts and patient representatives), the Appraisal Committee produced preliminary advice that degarelix was recommended only for patients who are "at risk of impending SCC". However, in the NICE FAD, the wording of the recommendation was for "people with spinal metastases who present with signs or symptoms of SCC." The company, together with patient groups appealed this decision on the basis that the change in wording from the ACD to the FAD would substantially restrict and reduce the patient group who would be eligible to receive degarelix. The appeal was upheld on two points: firstly, that NICE failed to issue a second ACD following a substantial change to the preliminary recommendations that significantly reduces the number of eligible patients that can be treated with degarelix, and secondly, the decision in the FAD to restrict use of degarelix to patients with spinal metastases who have actual SCC (as opposed to those who are "at risk" of SCC) lacks transparency and fails to give adequate reasons.

Following the appeal, NICE commissioned additional work from members of the ERG, under the auspices of the NICE Decision Support Unit (DSU). The DSU carried out a rapid systematic review and economic assessment with the following objectives:

- To identify any relevant information on the rate of SCC in men with metastatic hormone-dependent prostate cancer or, if possible, those with spinal metastases.
- To explore the possibility of undertaking a subgroup analysis in men with spinal metastases and to perform an economic analysis if data are available to do so.

The DSU systematic review[17] found very limited evidence to assess the rate of SCC in the early stages of treatment with LHRH agonists or degarelix. The largest study located reported a rate of 0.96% for SCC occurring within the first 30 days of LHRH agonist therapy in men with metastatic disease.[18] Economic analyses using the Committee's preferred assumptions suggested that degarelix was not cost-effective for the subgroup with metastatic disease. While degarelix could be cost-effective for the subgroup with spinal metastases, there were insufficient data on the size of this subgroup and the rate of SCC in order to estimate an ICER.

On the 5th June 2015, NICE released a second ACD (ACD2) stating that "degarelix is not recommended for treating advanced hormone-dependent prostate cancer." The company submitted a response to ACD2 on 26th June 2015, and following a request for clarification from NICE, additional information was submitted by the company in September 2015. This response proposed the development of a clinically derived and workable definition for the subgroup suitable for treatment with degarelix. The company also provided a further review of cost-effectiveness of GnRH antagonists over agonists in the subgroup, taking into account the cost benefit of rapid symptom relief on hospital stay and a revised pricing policy aimed to reduce the acquisition cost of degarelix to enhance the cost-effectiveness in the defined populations. The response included statements of support from Prostate Cancer UK, The British Association of Urological Surgeons (BAUS), and the British Uro-oncology Group (BUG) and a Delphi consultation summary conducted at the BAUS annual meeting in June 2015 about the specific patient populations that would be most suitable for treatment with degarelix.

The ERG were requested by NICE to review the company's response to the ACD2.

The ERG's key points noted:

- There was a likelihood 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 included a number of vague definitions, e.g. systemic signs of cancer.
- No evidence was 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 was associated with uncertainty.
- The evidence supporting the number of days of hospitalisation was not well described and hence associated with uncertainty.
- The subgroup modelled in the new economic analysis presented was unclear and the economic model was not suitably parameterised for undertaking subgroup analyses.

4.4 Outcome of the 5th Appraisal Committee meeting

Following this process, the NICE recommendation was amended and the updated Final Appraisal Determination (FAD) stated that: "Degarelix is recommended 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." [16]

5. KEY METHODOLOGICAL ISSUES

A key methodological issue during this STA concerned subgroup definition and, in particular, difficulty in defining a higher risk subgroup who may receive increased benefit from degarelix compared with the target population in the scope. For example, the subgroup of patients suitable for treatment with degarelix resulting from the Delphi study included a number of vague definitions, e.g. systemic signs of cancer. Secondly, the economic model was not suitably parameterised for undertaking subgroup analyses.

A main driver in cost-effectiveness was the avoidance of SCC events. However, evidence on the risk of such events across different subgroups was limited and the evidence that was available was highly uncertain due to the rarity of such events. This STA has illustrated the importance of having a complete understanding of the cost and occurrences of AEs when such events are pivotal to cost-effectiveness estimates.

The work described in the DSU report included analyses relating to subgroups: metastatic disease and spinal metastases however, economic model inputs and assumptions relate to the scope population rather than the subgroups, so such analyses should be treated with caution.

6. CONCLUSION

Degarelix received a positive recommendation from NICE only for a specific subgroup of those with spinal metastases from the initial target population of people with advanced hormone-dependent prostate cancer and dependent on discounted drug cost available to the NHS in June 2016. The NICE recommendations for research website[19] also states that "further research is recommended to resolve uncertainties about the clinical effectiveness of degarelix compared with LHRH agonists such as leuprorelin, goserelin and triptorelin for treating advanced hormone-dependent prostate cancer, particularly in subgroups of people with pre-existing cardiovascular disease, people with skeletal (including spinal) metastases and people with impending ureteric and urethral obstruction. Research should be planned as part of well-conducted randomised clinical trials."

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Contributions of the authors

Lesley Uttley drafted the final version of the manuscript and takes responsibility as the overall guarantor of the content. Sophie Whyte, Timothy Gomersall, Shijie Ren, Ruth Wong, Duncan Chambers and Paul Tappenden revised the manuscript for intellectual content. All authors have given their approval for the final version to be published. This summary has not been externally reviewed by PharmacoEconomics.

Compliance with Ethical Standards

Conflicts of interests

The authors LU, SW, TG, SR, DC, RW and PT have no conflicts of interest.

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