NICE National Institute for Health and Care Excellence

NICE guidance

Degarelix for treating advanced hormone-dependent prostate cancer

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 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.

1.2 This guidance is not intended to affect the position of patients whose treatment with degarelix was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Degarelix (Firmagon, Ferring Pharmaceuticals) is a selective gonadotrophin-releasing hormone antagonist that reduces the release of gonadotrophins by the pituitary, which in turn reduces the secretion of testosterone by the testes. Gonadotrophin-releasing hormone is also known as luteinising hormone-releasing hormone. Because gonadotrophin-releasing hormone antagonists do not produce a rise in hormone levels at the start of treatment, there is no initial testosterone surge or tumour stimulation, and therefore no potential for symptomatic flares. Degarelix has a marketing authorisation in the UK for the 'treatment of adult male patients with advanced hormone-dependent prostate cancer'. It is administered as a subcutaneous injection.

2.2 The most common adverse reactions with degarelix are related to the effects of testosterone suppression, including hot flushes and weight increase, or injection site reactions (such as pain and erythema). For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The starting dose of degarelix is 240 mg administered as 2 subcutaneous injections of 120 mg each, and the monthly maintenance dose is 80 mg administered as 1 subcutaneous injection. The cost of 2×120-mg vials is £260.00 and an 80-mg vial is £129.37 (excluding VAT; BNF 3rd May 2015). The company's estimate of a total course of treatment (including administration) is £12,306. The company estimated that, assuming treatment with degarelix continues until disease progression, the total time spent on treatment is 5.9 years (including time spent having combined androgen blockade and anti-androgen withdrawal). Costs will increase to approximately £14,800 assuming treatment with degarelix continues until death (including administration and anti-androgen withdrawal). The company has agreed a nationally available price reduction for degarelix with the Commercial Medicines Unit. The company also has a commercial scheme available to clinical commissioning groups. The reduced prices are commercial in confidence.

3 Evidence

The appraisal committee considered evidence submitted by Ferring Pharmaceuticals and reviews of these submissions by the evidence review group (ERG) and the Decision Support Unit (DSU). See the committee papers for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of degarelix, having considered evidence on the nature of advanced hormone-dependent prostate cancer and the value placed on the benefits of degarelix by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The committee discussed the current management of advanced hormone-dependent prostate cancer. It heard from the clinical experts that luteinising hormone-releasing hormone (LHRH) agonists (leuprorelin, goserelin and triptorelin) are first-line treatments for hormone-dependent prostate cancer, and that clinicians consider each LHRH agonist to have equivalent clinical efficacy. The clinical experts also stated that, in clinical practice, treatment with LHRH agonists continues after the disease has progressed and until death. The clinical experts noted that the treatment pathway for people with advanced prostate cancer is changing: hormonal treatment is being given earlier, drugs such as enzalutamide and abiraterone are used after disease progression, and treatment with abiraterone is increasingly being considered before chemotherapy in the treatment pathway. The committee noted the updated treatment pathway presented by the company in the submission of additional evidence; this positioned abiraterone before docetaxel, and enzalutamide before chemotherapy and abiraterone. The committee understood that although there may be variation in clinical practice, the updated treatment pathway presented by the company was not consistent with NICE guidance at the time of the appraisal (NICE technology appraisal guidance on abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen and enzalutamide for treating metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen). The committee heard from the clinical experts that the appropriate place for degarelix in the treatment pathway is as an alternative to LHRH agonists. The committee noted comments received during consultation that indicated the usefulness of having guidance for ongoing treatment with hormonal therapy once testosterone levels have been suppressed to castration levels with degarelix, and the possibility of switching to LHRH agonists afterwards in the interests of cost savings. The committee noted that it can only make recommendations on the technology under appraisal and

within the boundaries of its marketing authorisation. The committee considered that the likely position of degarelix in the treatment pathway is as first-line hormonal therapy for treating advanced hormone-dependent prostate cancer; that is, at the same point in the pathway as the LHRH agonists.

4.2 The committee heard from the clinical experts that degarelix is particularly appropriate for people at high risk of disease progression (who have a prostate-specific antigen [PSA] level of more than 20 ng/ml), older people, those with pre-existing cardiovascular disease, and people with spinal metastases from the prostate (some of whom may go on to develop spinal cord compression). The committee acknowledged that the NICE guideline on metastatic spinal cord compression states that symptoms suggestive of metastatic spinal cord compression may include: progressive pain in the spine, severe unremitting spinal pain, spinal pain aggravated by straining, pain described as 'band-like', localised spinal tenderness, nocturnal spinal pain preventing sleep, neurological symptoms such as radicular pain, limb weakness, difficulty in walking, sensory loss, and bladder or bowel dysfunction. It also states that if a patient with a diagnosis of cancer has neurological symptoms or signs suggestive of metastatic spinal cord compression, an MRI scan should be arranged within 24 hours and occasionally sooner if there is a pressing clinical need for emergency surgery. The committee concluded that consideration should be given to the subgroups highlighted by the clinical experts; that is, people at high risk of disease progression (who have a PSA level of more than 20 ng/ml), older people, those with pre-existing cardiovascular disease, and people with spinal metastases from the prostate (some of whom may go on to develop spinal cord compression).

4.3 The committee heard from the patient experts that people want to avoid the adverse events and discomfort associated with the later stages of prostate cancer. Patient experts stated that advanced prostate cancer is a diverse disease and people respond differently to treatments, so the availability of a range of treatment options is important. The committee heard from the patient experts that degarelix appears to offer long-term clinical benefit, which is particularly important for people with advanced disease. They also noted that the safety profile of degarelix is comparable to that of the LHRH agonists and the potential benefits of degarelix outweigh the adverse effects associated with it. Patient experts noted that subcutaneous injections of degarelix are administered monthly and this dosing schedule may be inconvenient for some patients

compared with the administration of LHRH agonists which is every 3 months. The committee concluded that degarelix may offer an additional option for people with advanced hormone-dependent prostate cancer.

4.4 The committee discussed the decision problem presented in the company's submission. It noted that the appraisal scope listed bicalutamide monotherapy as a comparator, but this comparison was not included in the company's submission. The committee noted that the company did not identify any head-to-head trial evidence comparing degarelix with bicalutamide monotherapy. It noted the evidence review group's (ERG's) comment that it may have been possible to conduct a naive indirect comparison. The committee heard from the clinical experts that in clinical practice, treatment with bicalutamide monotherapy is limited to a very small group of people, particularly those for whom preservation of sexual function is important and those who are willing to accept the adverse effects of the treatment, such as reduced overall survival and liver problems. The committee concluded that, based on the available evidence and UK clinical practice, it supported the company's view that comparing degarelix with bicalutamide monotherapy was not appropriate.

Clinical effectiveness

4.5 The committee considered the main clinical effectiveness evidence for degarelix compared with leuprorelin from the CS21 randomised controlled trial and the CS21A extension study. It also considered the evidence presented by the company from randomised controlled trials of degarelix compared with other LHRH agonists (CS28, CS30, CS31, CS35 and CS37). It heard from the clinical experts and the ERG that in clinical practice, people having hormonal therapy with LHRH agonists also have 28 days treatment with bicalutamide for protection against testosterone flare. The committee noted that in CS21 only 11% of patients in the leuprorelin group had flare protection with bicalutamide and it considered this to be inconsistent with UK clinical practice. The committee also noted that the 6 trials of degarelix compared with LHRH agonists included patients with all stages of prostate cancer, and that a large proportion of these had non-classifiable prostate cancer (approximately 19% of the patients in CS21). The committee also noted that some of the trials included in the company's submission used unlicensed doses and regimens of degarelix, which may have

had an impact on the results of these studies. The committee concluded that the generalisability of the trials' results to UK clinical practice was limited.

4.6 The committee discussed the clinical effectiveness results presented in the company's submission. It noted that all 6 studies were open label and primarily designed as non-inferiority trials and that the primary end point in the main clinical trial (CS21) was suppression of testosterone levels. It noted that in CS21 the licensed dose of degarelix (240/80 mg) resulted in a rapid suppression of testosterone to castration levels compared with leuprorelin, and that fewer patients had testosterone flare with degarelix than with LHRH agonists. It also noted that a non-inferior probability of achieving testosterone levels of 0.5 ng/ml or less from days 28 to 364 was observed for degarelix compared with LHRH agonists. The committee concluded that degarelix was non-inferior to LHRH agonists in suppressing testosterone levels and acknowledged that it is beneficial for avoiding testosterone flare. This is particularly important in people with spinal metastases from the prostate, some of whom may develop spinal cord compression, because there may be a relationship between the testosterone flare when hormonal treatment starts and spinal cord compression.

4.7 The committee considered the results from CS21 for the PSA progression end point. It noted that there was a statistically significant difference between degarelix and leuprorelin for the median percentage change in PSA levels. The committee also noted that post-hoc analyses of subgroups from CS21 showed that there was no statistically significant difference between treatment groups in the proportion of patients with metastatic disease who experienced PSA progression, and this was also similar in patients with locally advanced disease. The committee noted the post-hoc analyses of CS21 published by Tombal et al. (2010) that showed a statistically significant difference between degarelix and leuprorelin for PSA progression or death, but when adjusted for baseline PSA levels and disease stage this difference was no longer statistically significant (hazard ratio [HR] 0.664 [95% CI 0.385 to 1.146]). The committee heard from the clinical experts that it was not possible to say whether a difference in PSA progression is observed for degarelix compared with LHRH agonists in clinical practice. The committee noted the company's statement in the submission of additional evidence that the results of the CS21A extension trial supported the statistically significant difference in PSA progression-free survival between degarelix and leuprorelin. It also noted the ERG's comment that this difference

between degarelix and leuprorelin was not in fact demonstrated in CS21A, because it was a single arm trial (that is, it did not include a comparator group) and all patients who had leuprorelin in CS21 switched from leuprorelin to degarelix. The committee noted the results of the company's pooled analyses from the company's original submission, together with the results of the meta-regression analyses for PSA progression-free survival (using data from CS21 and CS35) which were presented in the company's submission of additional evidence. It was aware of the ERG's comments that pooled analyses should be interpreted with caution and that the company's meta-regression analyses had substantial limitations (including that it was unclear whether the definition of PSA progression-free survival was the same in the 2 trials). The committee discussed the differences between a random-effects model and a fixed-effects model for the meta-regression analyses. It understood that, although the point estimate overall would be expected to be similar in both models, the random-effects model assumes that each trial may estimate different treatment effects. The observed variation is therefore likely to be higher than for the fixed-effects model, because it includes both the sampling error and an estimation of the heterogeneity of the trials. The fixed-effects model assumes that all trials estimate the same treatment effect and any observed variation is simply the result of sampling error. The committee noted that the random-effects model gives a truer estimate of the underlying variability than the fixed-effects model when there is heterogeneity between trials. The committee noted that the trials included in the meta-regression analyses differed in terms of the doses of degarelix used (CS35 included an unlicensed dose), the inclusion criteria, the duration of follow-up and the primary end points. The committee accepted that because a random-effects model includes both the sampling error and an estimation of the heterogeneity of the trials, it would have been more appropriate for conducting the meta-regression analyses. The committee agreed with the ERG's comments and further noted that the analyses were not pre-specified and were conducted post hoc. The committee also noted that the results from the meta-regression analyses showed that the difference between degarelix and LHRH agonists in PSA progression-free survival for people with PSA levels of more than 20 ng/ml at baseline and for people with locally advanced or metastatic prostate cancer was not statistically significant. In addition, it noted that the ERG stated that the company's claim that the benefit of degarelix will be roughly equivalent or greater in people with PSA levels of more than 20 ng/ml at baseline than the observed hazard ratio is misleading because the company had

already adjusted for baseline PSA level. The committee considered that the results for PSA progression and long-term PSA progression benefit for degarelix compared with LHRH agonists were highly uncertain. It concluded that no PSA progression benefit from degarelix compared with LHRH agonists could be assumed and therefore this proposed subgroup of people at high risk of disease progression (that is, people with PSA levels of more than 20 ng/ml at baseline) was not considered further.

4.8 The committee discussed the results of the company's mixed treatment comparison for overall survival, and the ERG's comments and revised mixed treatment comparison. The committee noted that the duration of the trials was short and they were not sufficiently powered to detect differences in overall survival between treatments. It further noted that the absolute number of deaths in the trials was small. The committee also noted that the results of the company's mixed treatment comparison did not show statistically significant differences in overall survival for degarelix compared with each of the LHRH agonists and between the different LHRH agonists themselves. It noted the company's conclusion that the results showed equivalent clinical efficacy between LHRH agonists. The committee heard from the clinical experts that in clinical practice, all the LHRH agonists are regarded as having equivalent clinical efficacy, and no additional overall survival benefit has been observed with triptorelin compared with leuprorelin or goserelin. The committee concluded that it was plausible to assume equivalent clinical efficacy between LHRH agonists, but there was a lack of robust evidence to support an overall survival benefit with degarelix compared with LHRH agonists.

4.9 The committee discussed the results of the company's pooled post hoc analyses of adverse events from the 6 degarelix trials, and the meta-regression analyses for fractures that were presented in the company's submission of additional evidence. The committee noted the ERG's concerns about the robustness of the pooled analyses and the limitations of the company's meta-regression analyses (including appropriate preservation of randomisation, use of a fixed-effects model and an unlicensed dose of degarelix). The committee noted that the company acknowledged that the rate of fractures is likely to increase in people having either degarelix or LHRH agonists, and that the results from the meta-regression analyses showed no statistically significant difference between degarelix and LHRH agonists in reducing the risk of fractures. The committee also

considered the scenario analysis presented by the company in which the fracture risk was modelled with increased hazards for degarelix to give an equal risk of fractures to LHRH agonists at 2 years. The committee heard from the clinical experts and the ERG that the risk of fractures would be expected to increase in both groups over time as a result of a decrease in bone mineral density. The committee heard from the clinical experts that the duration of the trials was not long enough to demonstrate changes in bone mineral density and so these results should be considered exploratory. The committee concluded that there was a high degree of uncertainty about any difference in the rate of fractures for degarelix compared with LHRH agonists, and therefore no difference between fracture rates could be assumed between treatment groups.

4.10 The committee considered the results of the company's pooled analysis from its original submission and the meta-regression analyses for cardiovascular events that were presented in the company's submission of additional evidence. It noted the ERG's comments that the meta-regression analyses resulted in a hazard ratio that was more plausible in terms of statistical significance than the results of the company's original pooled analyses, but when compared with the results of the individual trials the result was implausible (the results had more favourable p values than the individual trials). The committee also noted that the results of a study by Albertsen et al. (2013) showed a statistically significant reduction in the risk of a cardiovascular event with degarelix compared with LHRH agonists in people with pre-existing cardiovascular disease. The committee noted comments received during consultation and the views of the clinical experts which suggested that degarelix may be particularly beneficial for people with pre-existing cardiovascular disease; treatment with LHRH agonists is associated with an increased risk of cardiovascular events because of changes in blood lipids, increased plasma insulin levels and increased risk of metabolic syndrome. The committee understood that the increase in conventional cardiovascular risk factors was due to androgen deprivation and was aware that degarelix, used within its marketing authorisation, was non-inferior to leuprorelin in producing androgen deprivation by suppressing testosterone to castration levels. The committee noted that the definition of cardiovascular disease in the company's analysis included a very broad composite outcome of several cardiovascular conditions (myocardial infarction, ischaemic cerebrovascular conditions, haemorrhagic cerebrovascular conditions, embolic and thrombotic events, and other ischaemic heart disease). It was also aware that cardiovascular events were

reported as adverse events in the study, and were not independent study end points. Furthermore, the patients included in the company's analysis were a subgroup of a subgroup and this reduced the power and robustness of the analysis and conclusions. The committee was aware of Albertsen et al.'s conclusion that, because their study had several limitations, the findings should only be interpreted as hypothesis-generating and that randomised controlled trials will be needed to validate the observations and define the mechanism by which they occur. The committee heard from the company that there are several hypotheses for the possible benefit of degarelix compared with LHRH agonists in reducing the risk of cardiovascular events in people with pre-existing cardiovascular disease, including suppression of both luteinising hormone and follicle-stimulating hormone and degarelix's potential effect of reducing inflammation linked with atherosclerosis. The committee noted comments received during consultation outlining the potential benefits of degarelix compared with LHRH agonists in people with pre-existing cardiovascular disease, and discussed in detail the clinical evidence presented for this subgroup. It concluded that, because of the uncertainty around both the pooled analyses and the meta-regression analyses presented by the company, and the lack of robust evidence confirming the effect of degarelix on reducing the risk of cardiovascular events compared with LHRH agonists, it was not possible to conclude that degarelix would reduce the risk of cardiovascular events in people with pre-existing cardiovascular disease compared with LHRH agonists.

4.11 The committee heard from the clinical experts that there may be a relationship between the testosterone flare when hormonal treatment starts and spinal cord compression in people with spinal metastases from the prostate. The risk of spinal cord compression may be lower in people having degarelix compared with LHRH agonists because degarelix does not produce an initial flare in testosterone levels. The clinical experts acknowledged that degarelix is not a treatment for spinal cord compression but agreed that it may provide an additional clinical benefit for the subgroup of people with spinal metastases from the prostate who may develop spinal cord compression. The committee explored the wording in the previous NICE guideline on metastatic spinal cord compression (now replaced by the NICE guideline on spinal metastases and metastatic spinal cord compression). It asked for the views of the experts and the company on whether the signs and symptoms suggestive of spinal cord compression, as specified in the guideline, would help to accurately define a subgroup of people who may

develop spinal cord compression. The committee heard from the patient experts that some of the symptoms specified in the guideline are not only associated with metastatic spinal cord compression but are quite common in people with prostate cancer. The committee also heard from some of the patient and clinical experts that it would not be appropriate to wait until people present with signs and symptoms that could be suggestive of spinal cord compression to start degarelix, because it is not a treatment for spinal cord compression and any benefit would be limited at this stage in the disease process which would be too late for preventing the event. The committee recalled comments received during consultation and clinical advice to the ERG that degarelix could be useful for people with actual or impending spinal cord compression from the prostate (that is, people who present with signs and symptoms of spinal cord compression) because it could not exacerbate spinal cord compression, since it does not produce a testosterone flare. 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. The difference in clinical benefit from these 2 approaches was unknown. The committee also heard from the clinical experts that in clinical practice there can be delays in access to an immediate MRI scan and that many people would not be seen by a specialist at disease presentation as stated in the guideline (see section 4.2), so these people cannot be easily and quickly identified. The clinical experts also noted that it would not be appropriate to do an MRI scan for all patients with spinal metastases from the prostate. The clinical experts acknowledged the difficulty in identifying bone metastases that may lead to spinal cord compression, and that this is exacerbated when attempting to identify metastases from the prostate that would lead to spinal cord compression solely as a result of a testosterone flare associated with LHRH agonists. The committee heard from the clinical experts that spinal cord compression can occur as a result of a single metastasis in the spine and also in people with more extensive disease. The patient and clinical experts also noted that they were not aware of any other tests or methods that would distinguish a subgroup of people with spinal metastases from the prostate who may develop spinal cord compression. The experts acknowledged that there is no evidence to support the use of degarelix in this subgroup beyond their experience in clinical practice. They noted that spinal cord compression caused by metastases from the prostate was an uncommon event and therefore it is difficult to estimate its incidence across

clinical practice in England. The patient experts noted that a clear definition of the patient population is needed, with a simple definition being preferred. The committee understood from the company and from the clinical and patient experts that degarelix would be considered suitable for all people with prostate cancer and spinal metastases, because they may develop spinal cord compression. The committee concluded that, although degarelix could offer particular benefit for people with spinal metastases who may develop spinal cord compression (because, unlike LHRH agonists, it does not produce an initial surge in testosterone levels, which is potentially associated with spinal cord compression), it is difficult to identify which people with spinal metastases would develop spinal cord compression directly as a result of the testosterone surge that can occur with LHRH agonists. The committee concluded that it is not possible to reliably identify and precisely define a subgroup of patients who face a higher risk of developing spinal cord compression from the broader population of patients with spinal metastases from the prostate.

4.12 The committee noted the NICE Decision Support Unit (DSU)'s work on the subgroup of people with metastatic hormone-dependent prostate cancer with spinal metastases from the prostate. It noted that this specifically explored the estimate of the rate of spinal cord compression in this subgroup with metastatic hormone-dependent prostate cancer with spinal metastases from the prostate. The committee noted that the DSU did not find any new evidence that would help the committee to better identify and clearly define the subgroup of people with spinal metastases from the prostate who may develop spinal cord compression as a result of testosterone flare associated with LHRH agonists and who might benefit most from degarelix. It specifically noted that the DSU did not find any evidence in the subgroup of patients with spinal metastases from the prostate and that based on an autopsy study that was subject to substantial limitations it derived with high uncertainty the estimated rate of spinal cord compression in this subgroup (1.35%). The committee was aware of the DSU statement that because of the high degree of uncertainty on the rate of spinal cord compression in people with spinal metastases any analysis based on this estimate should be considered with caution. Therefore the committee considered that this estimate was not robust enough to use for decision-making in this subgroup. The committee also noted that the DSU confirmed that the best evidence available for the rate of spinal cord compression in people with locally advanced or metastatic hormone-dependent prostate cancer remained the study by Oh et al. (2010; rate

of spinal cord compression of 0.96%) and it heard from the clinical experts that they were not aware of any other evidence apart from this study. The committee concluded that the work presented by the DSU provided further confirmation of the fact that it is not possible to clearly identify and define a subgroup of people who may develop spinal cord compression as a result of a testosterone flare from those people with spinal metastases from the prostate, and that the best evidence available for estimating the rate of spinal cord compression in people with metastatic hormone-dependent prostate cancer was the study by Oh et al.

Cost effectiveness

4.13 The committee discussed the cost-effectiveness evidence presented in both the company's original submission and the submission of additional evidence (which was received in response to consultation) for people with advanced hormone-dependent prostate cancer. The committee noted that clinical-effectiveness data for the model were derived from CS21, CS21A and CS35, and that the data for adverse events were derived from the meta-regression analyses. The committee was aware of its previous discussion about the equivalent clinical efficacy between LHRH agonists (see section 4.8) and concluded that it was plausible to assume equivalent clinical efficacy between LHRH agonists in the model.

4.14 The committee discussed the clinical effectiveness data for PSA progression used in the company's model. It was aware that PSA progression was the main driver of disease progression in the model, but it had concluded that a PSA progression benefit for degarelix compared with LHRH agonists was highly uncertain (see section 4.7). The committee concluded that the company's assumption of differential PSA progression for degarelix compared with LHRH agonists was not proven.

4.15 The committee considered the company's assumption of a link between PSA progression on first-line treatment and an increased risk of mortality for people with metastatic disease in the economic model. Assuming that there was a link, delayed progression from the first-line treatment states would result in a lower mortality risk, and therefore an overall survival benefit for degarelix compared with goserelin. It noted that in CS21 there was no statistically significant difference between degarelix and leuprorelin for PSA progression or death after

adjusting for baseline PSA level and disease stage. It also noted the ERG's concern that, because of the short duration of CS21 and because it was not powered to detect differences in survival, it was not appropriate to extrapolate the relationship between PSA progression and overall survival over a long time horizon based on the trial data. The clinical experts stated that, although PSA progression is a good indicator of treatment response, caution should be taken when using it as a surrogate outcome for extrapolating long-term overall survival. The committee acknowledged that there was no robust evidence to support any overall survival benefit for degarelix compared with LHRH agonists (see section 4.8) and concluded that no overall survival benefit for degarelix compared with LHRH agonists should have been assumed in the model.

4.16 The committee noted that the results of the company's meta-regression analyses for fractures, joint-related signs and symptoms, and cardiovascular events were used in the economic model. It was aware that these analyses lacked robustness and that there was a high degree of uncertainty around the results (see sections 4.9 and 4.10). It noted that the results of the company's meta-regression analyses showed no statistically significant difference between degarelix and LHRH agonists in reducing the risk of fractures. It also noted that the results of the company's meta-regression analyses for cardiovascular events were implausible when compared with the results of the individual trials (see section 4.10), and that the results of the study by Albertsen et al. (2013) should be interpreted with caution due to the limitations of the study. The committee further noted that when extrapolating the results over a long time horizon, the assumed benefit of degarelix was even greater. The committee concluded that there was considerable uncertainty around the estimated differences in the rates of fractures and cardiovascular events for degarelix compared with LHRH agonists. Therefore, it would have been more appropriate to assume no differences for the rate of cardiovascular events and fractures between degarelix and LHRH agonists in the model.

4.17 The committee discussed the updated utility values that were applied in the company's model and included in the submission of additional evidence in response to consultation. It noted that the company's updated model used the mapping algorithm from McKenzie and van der Pol (2009), which the committee had agreed was the most appropriate method to transform health-related quality-of-life data into utility values at its first meeting. This was because it included

around 20 times as many observations as the Kontodimopoulos et al. (2009) algorithm used in the company's original model, it had been validated by external data sources (thereby improving its generalisability), and it used all the EORTC QLQ-C30 domain scores in the equation to predict EQ-5D utility scores. The committee noted that the impact of using the McKenzie and van der Pol algorithm on the incremental cost-effectiveness ratio (ICER) for degarelix compared with LHRH agonists was small. The committee concluded that using the utility algorithm by McKenzie and van der Pol was an appropriate change to the model.

4.18 The committee considered the changes in the updated economic model and agreed with the ERG's assumption of hormonal therapy continuing until death in line with clinical practice. The committee also agreed with the ERG that it was not appropriate to use the results from the meta-regression analyses because of their limitations (see section 4.9) and the changes in the treatment pathway, because including the use of enzalutamide and abiraterone before docetaxel was not consistent with NICE guidance at the time of the appraisal.

4.19 The committee discussed the company's updated cost-effectiveness results from the economic model for people with advanced hormone-dependent prostate cancer. It noted that in the company's submission of additional evidence in response to consultation, the company had presented a probabilistic estimate of the ICER, 2 base-case scenarios (an updated base case and the company's conservative base case) and cost-effectiveness estimates for different subgroups. The committee noted that in the company's updated base-case analysis for degarelix compared with LHRH agonists, the ICER was £2,730 per quality-adjusted life year (QALY) gained. It noted that these results were still based on assumptions of greater clinical efficacy in terms of PSA progression, overall survival, reducing fracture rates over the first 2 years, and reducing cardiovascular events with degarelix compared with LHRH agonists. It noted its earlier conclusions that the evidence informing these assumptions was subject to a high degree of uncertainty. The committee also noted the ERG's comments that in the company's conservative base-case analysis, the company excluded the risk of fractures in both groups in the model (instead of assuming the same rate in both groups), and the committee considered this to be inappropriate. Therefore, the committee concluded that the company's conservative base case was not appropriate for decision-making. It further concluded that the company's updated base-case ICER was still based on implausible assumptions that were

likely to underestimate the true incremental cost per QALY gained of degarelix compared with LHRH agonists.

4.20 The committee considered the ERG's assumptions used in its original exploratory analyses. It noted that the ERG used triptorelin as the comparator in its base-case analysis, based on the results of its mixed treatment comparison and because it was the least costly LHRH agonist. The committee was aware of the comments from the clinical experts that all LHRH agonists were regarded as having equivalent clinical efficacy. The committee agreed with the ERG that it was plausible to assume that treatment with degarelix and LHRH agonists would continue until death based on the clinical experts' opinion on current UK clinical practice. The committee considered the ERG's assumption of no difference in PSA progression between degarelix and LHRH agonists and was aware of its earlier conclusion that the evidence to support any overall survival benefit for degarelix compared with LHRH agonists was highly uncertain (see section 4.15). It therefore concluded that no differences in PSA progression or death should be assumed in the model. The committee considered, based on the clinical experts' statements and the ERG's comments, that the proportion of people having chemotherapy in clinical practice would be lower than the 70% assumed in the ERG's exploratory analyses, and it understood that this proportion would represent an upper limit. The ERG mentioned that changes to these proportions did not have a large impact on the ICER. The committee noted the ERG's comments that the assumptions applied in its additional exploratory analysis, which used the committee's preferred assumptions agreed at the first meeting (treatment with degarelix and LHRH agonists until death, no differences in PSA progression or death, and no differences in the rate of fractures and cardiovascular adverse events between degarelix and LHRH agonists) and which were used to formulate the committee's preliminary recommendations, were the most appropriate to inform decision-making. The committee noted that, in the ERG's additional exploratory analyses (using the list price for degarelix), the ICER for degarelix compared with 3-monthly triptorelin was £103,200 per QALY gained (using its preferred assumptions of no differences in PSA progression or death, and no differences in the rate of fractures and cardiovascular adverse events between degarelix and LHRH agonists). It also noted that the ICERs for degarelix when other LHRH agonists were considered ranged from £70,600 per QALY gained compared with monthly triptorelin to £105,400 per QALY gained compared with 6-monthly triptorelin. The committee noted that all ICERs for

degarelix for treating advanced hormone-dependent prostate cancer (that is, people with locally advanced or metastatic hormone-dependent prostate cancer) were outside the range normally considered to be a cost-effective use of NHS resources.

4.21 The committee noted comments received during consultation which highlighted that degarelix is particularly beneficial compared with LHRH agonists for older people, people with pre-existing cardiovascular disease, skeletal metastases, and impending ureteric and urethral obstruction, and that these subgroups should be considered. The committee noted that the company did not include any cost-effectiveness subgroup analyses and did not provide any estimate of the ICER for these subgroups. The committee was therefore unable to consider the cost effectiveness of degarelix compared with LHRH agonists in these subgroups.

4.22 The committee considered the company's approach to including spinal cord compression events in the model, and the ERG's exploratory analyses for the subgroup of patients with spinal metastases with impending or actual spinal cord compression. It heard from the clinical and patient experts that degarelix may be beneficial for people with spinal metastases from the prostate who may develop spinal cord compression. The committee noted that the clinical trials included in the company's submission reported only 1 spinal cord compression in the LHRH agonist group and that the company derived the rates of these events from Oh et al. (2010), as used in the model from Lu et al. (2011), for its economic model. The committee noted the ERG's comment that because of the lack of data on the rate of spinal cord compression, this was the best available source of data for this adverse event, but also noted that the company did not consider a subgroup analysis for this population. The committee noted that the company assumed in its model that only people having LHRH agonists could have spinal cord compression. The committee understood the clinical plausibility behind this rationale, but it noted that this assumption would only be relevant for spinal cord compression that occurred as a result of the flare associated with starting treatment with LHRH agonists (see section 4.11). The committee considered the ERG's exploratory analyses for people with spinal metastases with actual or impending spinal cord compression. This was a subgroup specified in the scope, and it was assumed that people having degarelix would not have spinal cord compression. The committee considered this assumption to be optimistic after hearing from the clinical experts that degarelix could reduce the incidence of

spinal cord compression associated with testosterone flare, but that it would not prevent all spinal cord compression. Based on the assumption of equivalent efficacy in terms of PSA progression and overall survival between degarelix and LHRH agonists, the QALY gain for degarelix could be higher compared with triptorelin because degarelix does not produce an initial testosterone flare and so would reduce the risk of associated spinal cord compression. The committee noted that the rate of spinal cord compression was unknown in this subgroup and that the ERG's additional exploratory analysis, assuming different rates of spinal cord compression in people having LHRH agonists, showed that degarelix could potentially be considered cost effective compared with triptorelin in this subgroup. The committee noted that this exploratory subgroup referred to people with actual or impending spinal cord compression. It also noted comments from clinical and patient experts that when people have actual or impending spinal cord compression (that is, when signs and symptoms of spinal cord compression are already present) treatment with degarelix would be considered to be too late, and degarelix would have limited clinical benefit at this stage in the disease process (see section 4.11). The committee concluded that degarelix is not a treatment for spinal cord compression and it would have limited clinical impact in terms of avoiding spinal cord compression in people with spinal metastases from the prostate who already have signs and symptoms of spinal cord compression.

4.23 The committee understood from the company and from the clinical and patient experts that degarelix is not a treatment for spinal cord compression but it would be considered most suitable for people with prostate cancer who have spinal metastases, because they may develop spinal cord compression. It also understood from the clinical experts that identifying people who may develop spinal cord compression directly as a result of a testosterone flare from the broader population of those with spinal metastases is very challenging. The committee noted the appeal panel's conclusion that efforts should be made to accurately define the patient population if the technology is to be approved for a particular patient group, so that the NHS will be able to effectively operationalise such a decision. The appeal panel stated that the guidance should be precise in its language and noted that any term used must be clearly defined and consistently and exclusively used to describe the group defined. The definition of the patient group should be very clear, not reliant on different interpretations of language, and capable of application in a routine clinical setting. The committee accepted the views of the company, clinical and patient experts that a potential

subgroup of people with spinal metastases from the prostate who may develop spinal cord compression as a result of testosterone flare may exist in clinical practice, and it discussed at length the ways in which this population could be identified and defined (see section 1). The committee also considered the company's Delphi panel study, but noted that it does not provide new evidence to allow identification of people who may develop spinal cord compression. It concluded that this subgroup could not be reliably identified beyond those people who have spinal metastases from the prostate. The committee was mindful that if this subgroup cannot be clearly identified and defined in clinical practice, degarelix is likely to be used in all people with spinal metastases. The committee was mindful that all of the ICERs presented for the overall population of people with locally advanced or metastatic hormone-dependent prostate cancer were outside the range normally considered to be a cost-effective use of NHS resources (see section 4.20). The committee considered the company's analyses submitted during consultation for people with spinal metastases whose disease needs rapid testosterone suppression, but it noted the ERG's concern about the assumptions applied in the model, and that the definition of the subgroup was vague and leads to considerable uncertainty around the size of the subgroup. The committee concluded that the company's analyses for people with spinal metastases was associated with significant uncertainty and was not appropriate to use for decision-making.

4.24 The committee discussed the DSU's economic analysis that varied the rate of spinal cord compression in the model. The committee noted that the DSU applied estimated rates of spinal cord compression that could be representative of the expected rate of spinal cord compression for the subgroup of people with spinal metastases from the prostate, who may develop spinal cord compression. The committee noted that the DSU stated that these analyses should be interpreted with caution because of the uncertainty of the estimated rates and because they used the same model and assumptions from the economic analysis for the whole population with locally advanced or metastatic hormone-dependent prostate cancer, which may not be appropriate for the subgroup analyses. The committee recalled its previous conclusion that the DSU estimated rate of spinal cord compression in people with spinal metastases from the prostate was subject to high uncertainty and it was not robust enough to use for decision-making in this subgroup (see section 4.12). The committee also noted that all the analyses used some assumptions from the original model that were considered clinically

uncertain or implausible: all patients having LHRH agonists had testosterone flare; spinal cord compression occurred solely as a result of testosterone flare; anti-androgen treatment with bicalutamide did not have an effect on reducing testosterone flare and thus reducing spinal cord compression; and no spinal cord compression occurred in patients having degarelix. The committee noted that the best evidence available showed that the estimated rate of spinal cord compression in people with metastatic prostate cancer was approximately 0.96% and that this was confirmed by the clinical experts at the meeting. The committee was aware that at a rate of spinal cord compression of 0.96%, and when applying the proposed discount to the list price, the ICERs for degarelix compared with LHRH agonists in people with locally advanced or metastatic hormone-dependent prostate cancer were outside the range which is normally considered to be a cost-effective use of NHS resources (see section 4.24).

4.25 The committee noted that degarelix is currently available to the NHS at a discounted price through existing mechanisms (a national branded framework agreement with the Commercial Medicines Unit for secondary care, and a commercial scheme available to clinical commissioning groups in for primary care). It was mindful that when the ERG used the DSU analysis and applied the same discounted drug cost as that available to the NHS at the time of appraisal, for an assumed rate of spinal cord compression of 0.96% (reflective of the estimated rate of spinal cord compression in people with metastatic prostate cancer) it resulted in ICERs of £27,862, £10,839 and £6,780 per QALY gained compared, respectively, with triptorelin (3-monthly), goserelin (3-monthly) and leuprorelin (monthly). The committee noted again that these analyses used some assumptions that were considered clinically uncertain or implausible (see section 4.24). However, it acknowledged the particular benefit of degarelix for people with advanced hormone-dependent prostate cancer with spinal metastases. The committee concluded that, based on the above considerations and the ERG's exploratory analyses, degarelix should be recommended for the population with advanced hormone-dependent prostate cancer with spinal metastases from the prostate, only if the commissioner can achieve at least the same discounted drug cost as that available to the NHS through the company's existing agreements in June 2016.

4.26 The committee discussed whether degarelix was innovative in its potential to make a significant and substantial impact on health-related benefits. The

company noted that it considers degarelix to be a step-change in therapy from the current standard of care (LHRH agonists) because it provides more rapid and improved disease control, lower risk of disease progression, improved survival, no testosterone flare with initial treatment and fewer cardiovascular events. The company stated that all relevant health-related benefits were included in the QALY calculation. The committee did not consider degarelix to be a step-change in managing advanced hormone-dependent prostate cancer. The committee concluded that there were no additional QALYs associated with degarelix that had not been incorporated into the economic model and the cost-effectiveness estimates.

4.27 The committee considered whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism, when appraising degarelix. The committee noted NICE's position statement in this regard, and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard from the company that the list price of degarelix does not reflect any impact from the PPRS payment mechanism and that although this would have an effect on the cost of degarelix it did not know how large this impact would be. The committee heard nothing substantial to suggest that there is any basis for taking a different view with regard to the relevance of the PPRS to this appraisal of degarelix. It therefore concluded that the PPRS payment mechanism was not relevant for its consideration of the cost effectiveness of degarelix.

5 Implementation

5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

5.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

5.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has advanced hormone-dependent prostate cancer with spinal metastases and the healthcare professional responsible for their care thinks that degarelix is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Recommendations for research

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.

7 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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