Final Appraisal Report

Degarelix (Firmagon®) for the treatment of advanced hormone-dependent prostate cancer

Ferring Pharmaceuticals Ltd

Advice No: 2109 – December 2009

Recommendation of AWMSG

Degarelix (Firmagon®) is not recommended for use within NHS Wales for the treatment of advanced hormone-dependent prostate cancer. The case for the cost effectiveness of degarelix (Firmagon®) has not been proven.

Statement of use:
No part of this advice may be used without the whole of the advice being quoted in full.

This report should be cited as:
1.0 RECOMMENDATION OF AWMSG:

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday 16th December 2009

The recommendation of AWMSG is:

Degarelix (Firmagon®) is not recommended for use within NHS Wales for the treatment of advanced hormone-dependent prostate cancer. The case for the cost effectiveness of degarelix (Firmagon®) has not been proven.
2.0 PRODUCT DETAILS

2.1 Licensed indication
Degarelix (Firmagon®) is a gonadotrophin releasing hormone (GnRH) antagonist indicated for treatment of adult male patients with advanced hormone-dependent prostate cancer\(^1\).

The company focuses its submission on the use of degarelix in patients with metastatic prostate cancer\(^2\).

2.2 Dosing
Following reconstitution, degarelix should be administered as a subcutaneous (SC) injection in the abdominal region. The initial recommended dose is 240mg, administered as two 120mg SC injections, followed by a monthly maintenance dose of 80mg administered as one SC injection. Dose adjustment is not required for the elderly or in patients with mild or moderate liver or kidney function impairment. Degarelix should be used with caution in patients with severe liver or kidney impairment, as these patient groups have not been studied\(^1\).

The therapeutic effect of degarelix should be monitored by clinical parameters and prostate specific antigen (PSA) serum levels. In the case that the patient's clinical response appears to be sub-optimal, it should be confirmed that serum testosterone levels are remaining sufficiently suppressed. See the Summary of Product Characteristics (SPC) for further details\(^1\).

2.3 Market authorisation date
17 February 2009\(^2\).

2.4 UK Launch date
23 March 2009\(^3\).

3.0 DECISION CONTEXT

Prostate cancer is the most common cancer in men, accounting for approximately 25% of the new cancer diagnoses in England and Wales\(^4\). It is primarily a disease of advancing age and there is a three-fold increase in incidence in black men compared to white men, irrespective of the country of origin. Overall, incidence is increasing and the age-standardised incidence rate of prostate cancer increased by an average of 49% in Wales between 1996 and 2004\(^4\). This increase in incidence is thought mainly to be due to the incidental discovery of prostate cancer following transurethral resection of the prostate (TURP) in men with presumed benign prostatic hypertrophy and, more recently, the use of PSA screening\(^5\).

In most cases, prostate cancer has a long preclinical phase between onset and the appearance of clinical symptoms. The survival time after a symptomatic diagnosis is also long\(^6\). A NICE Clinical Guideline on prostate cancer was issued in 2008, which recommended preferred treatment options depending on the stage of the disease\(^4\). In patients with localised prostate cancer, treatment options are influenced by individual clinical factors, prognostic factors of PSA level, Gleason score (refer to glossary) and clinical stage. Treatment options include active surveillance for those with low risk disease, through to radical treatment such as prostatectomy or radiotherapy in those with intermediate or high risk disease when long-term control is a realistic prospect. In patients with locally advanced disease, radiotherapy with adjuvant or neoadjuvant luteinising hormone-releasing hormone agonist (LHRHa) therapy is recommended\(^4\). In
patients with metastatic disease (i.e. that which has spread beyond the prostate and pelvic lymph nodes), androgen (testosterone) withdrawal can control the disease for several years. This may be achieved by surgical castration (bilateral orchidectomy), or by the use of chronic LHRHa therapy

Prostatic carcinoma is known to be androgen (testosterone) sensitive and responds to treatment that removes the source of androgen. Chronic LHRHa therapy with agents such as goserelin (Zoladex and Zoladex LA) and leuprorelin (Prostap 3 and Prostap SR) effectively inhibits the production of testosterone by the testes to the same extent as surgical castration. In patients with metastatic disease, survival outcomes are similar with surgical castration and with LHRHa therapy. However, upon initial administration of LHRHa therapy there is a transient increase in testosterone levels that may necessitate the use of short-term anti-androgen therapy to help prevent stimulation of tumour cells. It may take two to four weeks for serum testosterone to fall to castrate levels with these agents.

Degarelix is a selective GnRH antagonist which, in contrast to the LHRHas, does not induce an initial testosterone surge and tumour stimulation. This avoids the need for early anti-androgen therapy that may be required with LHRHa therapy. The Committee for Medical Products for Human Use (CHMP) considered this to be the major clinical added value of degarelix and makes it especially useful when a rapid reduction in testosterone level is of critical importance.

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness
Comparative data are available from a randomised, open-label, phase III, non-inferiority study (CS21), which found that, in patients with all stages of prostate cancer, monthly administration of the licensed dose of degarelix was effective at reducing the testosterone levels to castrate levels over a 12 month period. The difference between degarelix and monthly leuprorelin in the proportion of patients achieving this endpoint met the pre-specified criterion for non-inferiority. Secondary endpoint data indicate that treatment with degarelix resulted in more rapid suppression of testosterone levels and PSA levels, and avoided the initial surge in testosterone levels observed with leuprorelin. However, few patients in the leuprorelin arm received initial anti-androgen therapy to protect against initial testosterone surge, which may account for some of the differences observed in these biological markers of response during early treatment. Beyond one month there was no significant difference in PSA and testosterone suppression between treatments. Clinical outcomes of tumour response and survival have not been assessed. The most common adverse effects observed for degarelix were those expected from testosterone suppression. With the exception of first dose injection site reactions, there was little difference in treatment-related adverse events between degarelix and leuprorelin.

4.2 Review of the evidence on cost-effectiveness
A cost-utility analysis has been conducted to compare monthly degarelix against three-monthly goserelin plus initial anti-androgen therapy, in patients with metastatic cancer. In the base case analysis, the incremental cost per QALY gained is estimated as £11,496.

There are a number of limitations and uncertainties with the model. As comparative data against goserelin are not available, post hoc sub-group analysis data from metastatic patients in study CS21 has been used on the assumption that leuprorelin as used in the clinical trial adequately represents goserelin use in clinical practice. The company
submission describes the results of several detailed literature searches that it asserts support the appropriate application of leuprorelin data from study CS21 to modelled goserelin treatment. These, however, do not relate specifically to PSA failure rates, which are the main driver of efficacy in the model. Survival and quality of life are assumed to be independent of the first-line hormone treatment that is received. Efficacy data for subsequent therapies following failure of hormone therapy are assumed, based on mean durations and rates of response as suggested in the European Association of Urology guidelines. However, there appears to be some discrepancy in the assumed treatment durations for different lines of therapy in different versions of the same guidelines, which has the potential to significantly impact upon the time horizon of analysis and assumed life expectancy of patients, and the extrapolated efficacy of degarelix and goserelin. This is not explored in the deterministic sensitivity analyses that have been conducted.

5.0 LIMITATIONS OF DECISION CONTEXT

- The non-inferiority of degarelix compared with leuprorelin has been investigated in the phase III trial using biological markers of response rather than clinical endpoints indicative of a direct benefit. Tumour reduction and improved overall survival for patients with prostate cancer have not been demonstrated.
- Although the company and CHMP consider that degarelix may be especially useful when a rapid reduction in testosterone levels is of critical importance, such as those with spinal metastases with a risk of cord compression, there are no data presented to demonstrate particular advantages with degarelix treatment in such a population.
- Few patients who received leuprorelin in the phase III trial also received anti-androgen therapy. The clinical benefit for degarelix compared to leuprorelin plus anti-androgen in the initial phase of treatment has not been demonstrated.
- There are no comparative data for degarelix against LHRHAs other than leuprorelin, nor against orchidectomy.
- The economic evidence presented in the company submission relates only to patients with metastatic disease; other stages, such as locally advanced prostate cancer, are not considered.

6.0 CLINICAL EVIDENCE

The main efficacy and safety data presented in the company submission² are from a phase III, open-label, multi-centre, randomised, non-inferiority study (CS21) that evaluated subcutaneous (SC) degarelix at a starting dose of 240mg followed by monthly doses of 160mg or 80mg, in comparison to monthly intramuscular (IM) administration of 7.5mg leuprorelin in 610 patients with prostate cancer requiring androgen deprivation therapy.¹,¹⁰ Table 1A in Appendix 1 provides summary details of patient characteristics, and the efficacy results in relation to the 240mg/80mg degarelix regimen. As the 240mg/160mg degarelix regimen is not licensed¹, the results from this arm of the study are not discussed here.

Brief details of several phase II, dose-exploring studies that informed the degarelix regimens to be evaluated in the phase III trial are also provided in the company submission². These are non-comparative studies and are not further discussed here.
6.1 Clinical efficacy
6.1.1 Study CS21
This study compared degarelix at the licensed dose (240mg SC initially, followed by 80mg SC monthly; n=207) against monthly IM leuprorelin (7.5mg; n=201) in patients with any stage of prostate cancer and who were ineligible for radical (curative) treatment. Around 29% of patients had locally advanced disease and 20% had metastatic disease at baseline. The primary objectives were to demonstrate that degarelix is effective with respect to achieving and maintaining testosterone suppression to below 0.5 nanograms/mL (i.e. to castrate levels) during 12 months of treatment and, further, to demonstrate the non-inferiority of degarelix to leuprorelin. Secondary endpoints included measures of testosterone levels over time, effects on PSA levels, and quality of life.

Based on the intention-to-treat (ITT) population, the probability of achieving and maintaining testosterone levels ≤0.5 nanograms/mL between day 28 and day 364 (the primary endpoint of the trial) was 97.2% with degarelix and 96.4% with leuprorelin. The difference of 0.875% (97.5% confidence interval [CI]: -3.21 to 4.96) fulfilled the pre-specified criterion for demonstration of non-inferiority of degarelix to leuprorelin (the lower limit of the CI being greater than -10%).

Treatment with degarelix resulted in more rapid suppression of testosterone levels to ≤0.5 nanograms/mL compared with leuprorelin. By day 3, 96% of degarelix recipients had levels below 0.5 nanograms/mL compared with none in the leuprorelin arm, and by day 14, 100% of degarelix recipients had achieved this level of suppression compared with 18% in the leuprorelin arm. By day 28, 100% of patients in both arms had achieved suppression to castrate levels. No patients in the degarelix (240mg/80mg) treatment arm experienced an initial surge in testosterone levels (defined as testosterone level exceeding baseline level by at least 15%) during the first two weeks of treatment, compared with 80.1% of patients who received leuprorelin (p<0.0001).

PSA levels, considered to be an indirect measure of tumour response, were also reduced more rapidly with degarelix treatment compared with leuprorelin. On day 14, the median percentage change in PSA from baseline in the degarelix and leuprorelin arms was 63.4% and 17.9%, respectively (p<0.0001), and on day 28 was 84.9% and 66.7%, respectively (p<0.0001). From day 56 onwards there was no significant difference between treatment arms in the change from baseline.

The use of anti-androgen therapy in leuprorelin recipients was noted to influence the degree of PSA reduction. In patients who started anti-androgen therapy on or before day 7, median PSA levels were reduced by 61.7% on day 14 and 89.1% on day 28. In contrast, median PSA levels were only reduced by 15.3% on day 14 and 61.7% on day 28 for patients not taking anti-androgens. It should be noted few leuprorelin recipients received early anti-androgen therapy, which warrants caution in the interpretation of these figures. However, if PSA level is considered an indirect measure of tumour response, this highlights the potential value of the use of early, short term anti-androgen therapy in LHRHa recipients.

Patient quality of life (QoL) was assessed on days 0, 28, 84, 168 and at the end of study visit using the generic Short Form-12 v2 (SF-12-v2) and the cancer-specific EORTC QLQ-C30 questionnaires. There were no discernible differences in QoL from baseline or between treatment groups at any point in time.

The company also provided a series of post hoc analyses conducted in patients with different stages of prostate cancer and with different baseline PSA levels, which remain commercial in confidence.
Points to note:

- This was an open-label trial due to the different routes of administration of study treatments; however, central laboratory personnel were blinded to treatment assignment\(^\text{10}\).
- In this trial, leuprorelin was administered IM once monthly at a dose of 7.5mg\(^1,\text{10}\). However, the leuprorelin SPCs recommend a dose of 3.75mg once monthly (either SC or IM) for the Prostap SR\(^\circledR\) product\(^9\), or 11.25mg SC every three months for the Prostap 3 product\(^8\). Company-sought expert opinion is reported to indicate that patients with metastatic disease would be likely to receive LHRHa therapy at three month intervals\(^2\).
- Non-inferiority has been investigated using surrogate outcome measures and not clinical endpoints indicative of a direct benefit.
- The use of initial anti-androgen therapy for protection against testosterone surge in the leuprorelin arm was low compared with that in patients receiving LHRHa therapy in clinical practice. Subgroup analysis indicated that PSA suppression may be substantially improved at day 14 and day 28 in those leuprorelin recipients who receive early concomitant anti-androgen therapy. The leuprorelin arm in study CS21 may, therefore, not adequately represent LHRHa use in clinical practice and may serve to overestimate the benefits of degarelix in terms of early PSA response.
- It should be noted that only 20% of patients in study CS21 had metastatic disease.
- *Post hoc* sub-group analyses indicate that the results for the primary endpoint were similar regardless of age, race, geographical location, stage of prostate cancer and patient weight, although there were some discrepancies in the sizes of the subgroups\(^10\).

6.2 Safety

In study CS21, similar proportions of patients in the combined degarelix 240/160mg and 240/80mg, and leuprorelin groups experienced treatment-emergent adverse effects (TEAEs) (81% versus 78%). The most common TEAEs observed with degarelix were due to the expected physiological effects of testosterone suppression such as hot flushes (26%) and weight gain (7%), or injection site reactions such as pain (29%) and erythema (21%)\(^1,\text{10}\). Drug-related adverse events occurred in 58% of the degarelix groups compared with 42% of the leuprorelin group, the difference being due primarily to the higher incidence of injection site reactions with degarelix. Around 40% of all degarelix recipients experienced injection site reactions compared with one patient in the leuprorelin group. The incidence of reactions such as pain, erythema, and swelling specifically in the degarelix 240/80mg group was lower than in the degarelix 240/160mg group. These occurred primarily with the initial 240mg dose (32% of patients) and few patients (3%) experienced events with subsequent maintenance doses. Most were transient and mild to moderate, and very few (<1%) led to treatment discontinuation. The CHMP notes that the IM route of administration of leuprorelin may have contributed to its low incidence of injection site reactions in study CS21, and that SC administration of leuprorelin is associated with a high rate of injection site reactions\(^10\).

When injection site reactions were excluded, the incidence of drug-related adverse events was similar for degarelix 240/80mg (43%) and leuprorelin (42%)\(^10\). The incidence of serious adverse events was comparable between treatment groups (11% degarelix and 14% leuprorelin), and the most common serious adverse events were cardiovascular, and renal and urinary disorders. Long-term androgen deprivation therapy may prolong the QT interval and both degarelix and leuprorelin showed QT/QTcF intervals exceeding 450msec in approximately 20% of the patients. It is
important to note that patients with a history of or risk factors for QT prolongation, or taking medicines that may prolong the QT interval, were excluded from this study\textsuperscript{10}.

Changes in laboratory values during the study were in the same range for degarelix and leuprorelin. In patients with normal haematological values prior to treatment, marked decreases in haematocrit ($\leq 0.37$) and haemoglobin ($\leq 115$g/L) levels were observed (40\% and 13-15\%, respectively). It is unknown to what extent this decrease in haematological values was caused by the underlying prostate cancer and to what extent it was a consequence of androgen deprivation therapy\textsuperscript{1}.

The proportion of patients completing the study was considered to be comparable between treatment groups\textsuperscript{10} (82\% degarelix 240/80mg and 86\% leuprorelin). The incidence of non-fatal adverse events leading to discontinuation in the degarelix groups was 5.9\% compared to 1.5\% in the leuprorelin group. Death during treatment and within 30 days after the last dose occurred in 2.4\% of the degarelix patients (10 deaths) compared to 4.5\% of the leuprorelin group (9 deaths). No deaths were considered treatment-related\textsuperscript{10}.

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator treatment

In patients with advanced prostate cancer, treatment options may include radiotherapy with adjuvant or neoadjuvant LHRHa, or, in those with metastatic disease, androgen withdrawal by means of surgical castration (bilateral orchidectomy), or the use of chronic LHRHa therapy\textsuperscript{4}.

LHRHa therapy, usually in combination with short-term anti-androgen therapy, would be the appropriate comparator for degarelix. LHRHas include goserelin, leuprorelin, and triptorelin (Decapeptyl\textsuperscript{®} SR/Gonapeptyl\textsuperscript{®}). Early anti-androgen therapy to protect against initial testosterone surge may include cyproterone acetate, flutamide or bicalutamide\textsuperscript{11}. These agents would be commenced three days before initiating LHRHa therapy and continue for three weeks\textsuperscript{11}.

7.2 Comparative effectiveness

- Comparative data for degarelix are limited to study CS21, which demonstrated efficacy at its licensed dose in rapidly suppressing testosterone to castrate levels in patients with any stage of prostate cancer. Non-inferiority to monthly administration of leuprorelin 7.5mg was also confirmed in relation to testosterone suppression over 12 months of treatment\textsuperscript{10}.
- Only one year efficacy data are available for degarelix, and these relate only to surrogate outcomes; beneficial effects in terms of tumour reduction and survival have not been demonstrated. This is in contrast to LHRHas, which have supporting comparative survival data\textsuperscript{6-9,12}.
- Secondary endpoint data from study CS21 indicate that degarelix treatment leads to more rapid suppression of testosterone levels than leuprorelin and, in contrast to leuprorelin, is not associated with an initial surge in testosterone levels\textsuperscript{10}. The CHMP considered this to be the major clinical added value of degarelix treatment, and considered degarelix to be especially useful when a rapid reduction in testosterone levels is of critical importance\textsuperscript{10}. The European Association of Urology (EAU) guidelines\textsuperscript{13} note that early anti-androgen use reduces but does not completely remove the risk of clinical relapse associated with initial testosterone surges in patients using LHRHas. These guidelines recommend that, for patients with impending spinal cord compression, alternative strategies for completely ablating testosterone levels, such as bilateral orchidectomy or
LHRH antagonists, should be considered. However, it should be noted that there are no data presented to demonstrate particular advantages with degarelix treatment in such a population. Beyond 28 days, there was no significant difference in the degree of testosterone suppression with degarelix and leuprorelin.

- PSA levels are considered an indirect marker of tumour response. Degarelix leads to a more rapid reduction in PSA levels compared with leuprorelin, however the influence of this on long-term patient outcomes is unclear. It is of note that beyond 56 days there was no significant difference in reductions from baseline PSA levels, nor in the probability of completing the study without experiencing PSA failure.

- The use of initial anti-androgen therapy in the leuprorelin arm for protection against testosterone surge was low compared with that in patients receiving LHRHa therapy in clinical practice, and CHMP stated that the clinical benefit for degarelix compared to leuprorelin plus anti-androgen in the initial phase of treatment has not been demonstrated. Subgroup analysis indicated that PSA suppression may be substantially improved at days 14 and 28 in those leuprorelin recipients who receive early concomitant anti-androgen therapy, to a similar level as that observed with degarelix treatment. The limited use of anti-androgen therapy in the leuprorelin arm of study CS21 compared with routine clinical practice may, therefore, serve to overestimate the benefits of degarelix in terms of early PSA response. The company submission states that there is little evidence that short-term anti-androgen therapy for testosterone surge protection is likely to influence long-term patient outcomes.

- The extent to which the leuprorelin arm of study CS21 adequately represents the use of LHRHAs in clinical practice is unclear. In addition to the low rates of use of anti-androgen therapy, leuprorelin was administered at a dose of 7.5mg once monthly, which is not a licensed dose in Europe. Company-sought expert opinion is reported to indicate that patients with metastatic disease would be likely to receive LHRHa therapy at three month intervals rather than monthly. In addition, goserelin is reported in the company submission to be the most commonly used LHRHa in Wales. The company has conducted several literature searches, which it suggests indicate that there is little evidence of differences in outcomes between leuprorelin given at 7.5mg versus the licensed dose of 3.75mg monthly, or between leuprorelin given monthly versus three monthly, or between leuprorelin and goserelin.

- The incidence of treatment-related adverse events was greater with degarelix than with leuprorelin, primarily due to injection site reactions. The LHRHAs goserelin, leuprorelin and triptorelin are available in formulations that are licensed for administration at three-month intervals. In contrast, degarelix is only licensed for administration on a monthly basis, which would involve a greater number of injections over the course of treatment. However, study CS21 data suggest that injection site reactions with degarelix occurred primarily with the initial 240mg dose and few patients (<3%) experienced events with subsequent maintenance doses. When injection site reactions were excluded, the incidence of drug-related adverse events was similar for degarelix 240/80mg and leuprorelin.

- There were no discernible differences in quality of life at any time point between the two treatments in study CS21. However, in the trial both treatments were administered monthly and it should be considered that in practice the frequency of injections, which may require travel to a health care setting for administration by a health care professional, will be three times greater with degarelix compared with LHRHa therapy.
8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE

8.1 Overview of the key economic issues for AWMSG to consider
The key economic issue to consider is whether the additional benefits offered by degarelix over the relevant comparator(s) justify the additional costs and if so, whether the total budgetary impact of supporting the use of degarelix is acceptable (see section 9.0).

8.2. Description and critique of the company’s submission
The company submission describes a cost utility analysis of degarelix given monthly compared against the LHRHa goserelin given once every three months in the treatment of patients with hormone-responsive metastatic prostate cancer. All patients who receive goserelin are assumed to receive early anti-androgen therapy with bicalutamide. A Markov model has been developed in which patients receive first-line hormonal therapy until disease progression, defined as PSA failure as per the phase III study CS21, or for a maximum of 36 months. Following disease progression, patients enter a second health state in which they move through a treatment algorithm of sequential therapy based on potential therapeutic options described in the EAU guidelines on prostate cancer, followed by palliative care. This treatment algorithm dictates the maximum lifetime in the model as 80 months and, in each three-month cycle, patients are at risk from prostate cancer-specific death or death from any other causes.

There are a number of limitations and uncertainties to the model that is described. Efficacy data used in the model for first-line hormone therapy is PSA failure data derived from post hoc subgroup analyses in patients with metastatic disease in study CS21 (see section 6.0). This assumes that outcomes from patients taking an unlicensed monthly dose of leuprorelin, with very low use of early anti-androgen therapy, is adequately representative of goserelin – used at the licensed dose of every three months in patients who all receive early anti-androgen therapy routinely. The company submission describes the results of several detailed literature searches that it asserts support the appropriate application of leuprorelin data from study CS21 to modelled goserelin treatment. However, a limitation of these is that they relate to key outcomes of survival. In the model, survival is assumed to be independent of treatment received, and it is PSA failure rates that drive progression through the modelled health states for degarelix and goserelin. Efficacy data for subsequent therapies following failure of hormone therapy are assumed, based on mean durations and rates of response as suggested in the EAU guidelines. However, there appears to be some discrepancy in the assumed treatment durations for different lines of therapy in different versions of the same guidelines, which has the potential to significantly impact upon the time horizon of analysis and the extrapolated efficacy of degarelix and goserelin. Quality of life is assumed to be independent of treatment received. The economic model was not provided, and this precluded verification of the reported outputs.

8.3 Population
The patient group that is modelled consists of those with hormone-responsive, metastatic prostate cancer who are indicated for androgen deprivation therapy with LHRHa plus initial anti-androgen therapy for testosterone surge protection. The population is based on those in the phase III study CS21. Only around 20% of patients in this trial had metastatic disease at treatment initiation and in the whole population the use of anti-androgen therapy was low.
8.4 Perspective and time horizon
The analysis is conducted from the perspective of NHS Wales.

The company submission states that a lifetime horizon of analysis has been adopted. This has been calculated as 80 months (6.7 years) and is based on the sum of the mean duration of response to first-line hormone therapy and to subsequent lines of therapy listed in an algorithm in a version of the EAU guidelines\textsuperscript{13}, and informed by median survival for hormone-refractory prostate cancer patients initiated on chemotherapy (see section 8.5). There is another published version of these same guidelines\textsuperscript{15} and the algorithm within this version would lead to a significantly longer estimated maximum lifetime (see section 8.5 for further details). There would appear to be some uncertainty in the time horizon of analysis and the assumed life expectancy of patients.

Each cycle of the Markov model is three months and a half-cycle correction has been applied\textsuperscript{2}.

8.5 First-line comparator and treatments following first-line therapy failure
The comparator is the LHRHa goserelin, administered at three month intervals, plus initial anti-androgen therapy with bicalutamide 50mg daily for testosterone surge protection. On the basis of company market research, goserelin is by far the most commonly used LHRHa and bicalutamide is the most commonly used anti-androgen in Wales\textsuperscript{2}. Bicalutamide is assumed to be given to all goserelin recipients, starting three days before and continuing for three weeks after LHRHa initiation\textsuperscript{2}.

It is assumed that the maximum duration of first-line hormone therapy with either degarelix or goserelin is 36 months\textsuperscript{2}. This is based on the EAU guidelines quoting a mean duration of first-line hormone therapy\textsuperscript{13}. Following disease progression, patients enter a second health state in which they move through a treatment algorithm of sequential therapy based on potential therapeutic options described in the EAU guidelines on prostate cancer (see section 8.4)\textsuperscript{13}. The treatments listed in the EAU algorithm are considered as general options for patients with hormone-refractory disease in the NICE clinical guideline on prostate cancer\textsuperscript{4}. However, the NICE guideline stops short of recommending such a specific order or approach to their use\textsuperscript{4}. The evidence base for the algorithm in the EAU guidelines is unclear, and the EAU guidelines refer to the treatments included in the flow-chart as options, rather than as specific recommendations\textsuperscript{13}.

This EAU algorithm suggests that second-line therapy could involve the addition of anti-androgen therapy to degarelix or goserelin to attempt maximal androgen blockade, with a response rate of 60-80% and mean duration of response of four to six months. In the model the upper limits of rate and duration of response have been assumed for this and all subsequent treatments in the algorithm. Following the addition of anti-androgen, the treatment algorithm suggests\textsuperscript{13}:

- substitution of the anti-androgen (response rate 40%, mean duration of response six months),
- anti-androgen withdrawal (response rate 40%, mean duration of response six months),
- secondary hormonal manipulation with diethylstilbestrol (DES, response rate 60%, mean duration of response eight months),
- chemotherapy using docetaxel (response 70%, mean duration of response 12 months).
The NICE technology appraisal of docetaxel in hormone-refractory prostate cancer\textsuperscript{16} notes that median survival following initiation of docetaxel was observed in one trial to be 18.9 months. As the EAU treatment pathway suggests an upper value for mean duration of response to chemotherapy of 12 months, it is assumed in the company submission that following chemotherapy for 12 months, patients would survive for a further six months during which they would receive palliative care\textsuperscript{2}. The maximum length of survival is therefore estimated to be 80 months, and this is used to determine the time horizon of the analysis\textsuperscript{2}. It should be noted that a further publication of the same EAU guidelines presents higher upper estimates for mean duration of response for first-line hormone therapy (48 months), addition of anti-androgen therapy (8 months), secondary hormonal manipulation with DES (15 months) and chemotherapy (29 months)\textsuperscript{15}. The reason for these discrepancies is unclear but the implications are potentially significant. The sum of treatment durations, implied to represent maximum length of survival, increases to 124 months (10.3 years), which would increase the time horizon of analysis. In addition, the estimation of the probability of PSA failure with degarelix and goserelin could be significantly different (see section 8.6.1.1).

The company submission acknowledges that treatment options, response rate and duration of response are highly individual and variable for the modelled patient group. Company-sought expert opinion is reported to indicate that anti-androgen substitution is not common practice in Wales, and that some clinicians will use corticosteroids as stand alone therapy\textsuperscript{2}. However, in the absence of consensus, the company has continued with the use of this algorithm on the basis that it is a practical approach to modelling second-line and subsequent treatment for patients who fail first-line hormone therapy, which is based on recognised guidelines\textsuperscript{2}. As the Markov cycle is three months, patients who do not respond to treatment are assumed to remain on that treatment for the duration of the three month cycle before moving to the next treatment line or death\textsuperscript{2}.

8.6 Clinical inputs
8.6.1 Efficacy data
8.6.1.1 PSA failure rates in first-line hormone treatment
The main efficacy data used in the model are PSA failure rates, which determine transition from first-line hormone therapy to second and subsequent line therapy. These efficacy data for degarelix and goserelin are derived from post hoc sub-group analyses of the 12-month study CS21 in the 20% of patients who had metastatic disease at treatment initiation. The 12-month data have been extrapolated to up to three years in the model\textsuperscript{2}.

Study CS21 did not evaluate the LHRHa goserelin; it evaluated the LHRHa leuprolelin given at a monthly dose that is unlicensed in Europe, and very few patients in the study received initial anti-androgen therapy\textsuperscript{10} (see section 6.1 and 7.2). Therefore, a number of assumptions are made to model goserelin treatment as used in clinical practice. These are:

- There would be no difference in outcomes between leuprolelin given at 7.5mg monthly, as in study CS21, versus the licensed dose of 3.75mg monthly.
- There would be no difference in outcomes between leuprolelin given monthly, as in study CS21, versus three monthly as is used more often in clinical practice for patients with metastatic prostate cancer.
- The low levels of use of early anti-androgen therapy for protection against initial testosterone surge in LHRHa recipients study CS21 would not influence long term outcomes compared with the routine use of anti-androgen therapy in clinical practice.
- There are no differences in the outcomes between leuprolelin and goserelin.
The company submission contains details of several literature searches, which it suggests indicate that there is little evidence of differences in survival outcomes between leuprorelin given at 7.5mg versus the European licensed dose of 3.75mg monthly, or between leuprorelin given monthly versus three monthly, or between leuprorelin and goserelin. The strongest evidence identified for the equivalence of goserelin and leuprorelin in terms of survival is from a published systematic review and meta-analysis, which compared LHRHs against orchidectomy\textsuperscript{12}. This concluded that there was no evidence of differences in overall survival between the LHRHs goserelin, buserelin (Suprefact\textsuperscript{6}) and leuprorelin, but commented that the confidence intervals around the hazard ratio for leuprorelin were wide\textsuperscript{12}. Whilst overall survival is one of the most important endpoints for patients, in the model presented in the company submission survival is independent of the actual treatment received (see 8.6.1.3). The difference in efficacy between degarelix and goserelin that has been modelled is driven by differences in PSA failure rates and there are no data presented to directly support the assumption that PSA failure rates would be the same for goserelin and leuprorelin over the 12 months of follow-up from study CS21 that has been extrapolated to up to three years in the model.

In relation to the use of anti-androgen therapy to protect against initial testosterone surge, the company-conducted literature searches identified little data available to determine whether or not the early use of anti-androgen therapy influences long term outcomes in general\textsuperscript{2}. Study CS21 found that, overall, PSA levels were reduced more rapidly with degarelix treatment than with leuprorelin, but subgroup analysis indicated that PSA suppression may be substantially improved at days 14 and 28 in those leuprorelin recipients who receive early concomitant anti-androgen therapy, to a similar level as that observed with degarelix treatment (see section 6.1)\textsuperscript{10}. Across all patients, the change in PSA levels from baseline was not significantly different from day 56 onwards, and the overall probability of experiencing PSA failure over the 12 months was numerically but not statistically significantly different for degarelix compared with leuprorelin. The model relies on PSA failure rates in a subgroup of patients with metastatic disease (around 20% of the study population). The proportions of this subgroup that received initial anti-androgen therapy is not stated, and it is possible that PSA levels with leuprorelin therapy would have been improved in the first month had anti-androgen therapy been used routinely in these patients. However, the probability of PSA failure is estimated using data from the entire 12 month period of study CS21, and the extent to which the estimated probability of PSA failure would have changed for the leuprorelin arm with the short term use of anti-androgen therapy in the first month of treatment is uncertain. Sensitivity analysis around the probabilities of PSA failure at 12, 9 and 6 months with goserelin treatment indicate that the model is relatively sensitive to this parameter when explored within the range +/-25%, but the influence of the probability of PSA failure at three months with goserelin is not among the top 20 most influential parameter values that were tested\textsuperscript{2} (see section 8.9.2).

For patients with metastatic disease who received degarelix, the cumulative probability of not experiencing PSA failure was reported. This data remains commercial in confidence. The cumulative probabilities of PSA failure were converted to three-month probabilities and extrapolated to provide the probabilities of PSA failure in each three month period up to a maximum of 36 months, on the assumption that 100% of patients would experience PSA failure by 36 months\textsuperscript{2} (see section 8.5). This leads to the assumption that in each of the three month cycles up to 33 months, degarelix has a smaller probability of PSA failure (and hence a lower rate of switching to second and subsequent lines of therapy) than goserelin. The impact of the discrepancy in the duration of first-line hormone therapy between the different sources of the EAU guidelines\textsuperscript{13,15} (see section 8.5) is unclear and is not explored in the model. This would appear to be a significant source of uncertainty that may bias the model.
8.6.1.2 Efficacy of second and subsequent-line therapy
The efficacy of second and subsequent line therapy is simply based on the mean response rates and duration of response for the treatments in the EAU treatment algorithm\textsuperscript{13}. The impact of the discrepancy in the mean duration of response for these treatments between the two versions of this same guideline\textsuperscript{13,15} (see section 8.5) is unclear, but would apply to both treatment arms of the model.

8.6.1.3 Mortality
Within each three month cycle, patients are at risk of death due to prostate cancer or death from any cause. Death due to prostate cancer is modelled independently of treatment received. A previous economic analysis of androgen suppressive therapies\textsuperscript{17} is cited as providing a rate of progression from metastatic disease to death per person year of 0.524 (not verified), which has been converted into a constant three month probability of death due to prostate cancer. The annual rate of all cause mortality is based on National Statistics 2001 population estimates for England and Wales, from which constant three-month probabilities have been derived\textsuperscript{2}.

8.6.2 Adverse events
In study CS21, the incidence of treatment-related adverse events was greater with degarelix compared with leuprorelin, due to a greater incidence of injection site reactions. When injection site reactions were excluded, there was no significant difference in the incidence of adverse events\textsuperscript{10} (see section 6.2). It is implicitly assumed that there is no difference in adverse events between leuprorelin and goserelin.

8.6.3 Utility weights
Study CS21 measured health-related quality of life directly using generic and a cancer specific questionnaires\textsuperscript{10}. There was no difference in quality of life observed between degarelix and leuprorelin at any time point\textsuperscript{10} (see section 6.1). However, in the trial both treatments were administered monthly and it should be considered that in practice the frequency of injections, which may require travel to a health care setting for administration by a health care professional, will be three times greater with degarelix compared with LHRHa therapy.

The utility weights applied in the economic model are derived from the previous economic analysis of androgen suppressive therapy\textsuperscript{17}, which based its estimates on a review of the literature relating to prostate cancer-quality of life from the perspective of patients and physicians. Three utility weights have been derived relating to: patients receiving first-line hormone therapy; patients receiving continuous anti-androgen therapy, undergoing anti-androgen withdrawal, or receiving DES; and patients receiving chemotherapy or palliative care. These are applied in each three month cycle. For patients who experience injection site reactions, a 15% reduction in utility is applied, also for three months, which the company acknowledges is unrealistic but is a limitation of the use of the three month cycle, and is considered to be a conservative approach\textsuperscript{2}.

The utility values have been converted to monthly utility values and applied to the mean proportions of patients responding and not responding to each line of treatment. The proportions of patients who respond / do not respond to each line of therapy have been adjusted by the risk of death (due to prostate cancer or otherwise), but the fact that the durations of response in the model are based on mean durations of response and the response rates are expected rates as listed in the EAU guidelines\textsuperscript{13} may lead to a degree of double counting of the impact of death. The resultant adjusted proportions of responders and non-responders do not appear to sum to 100%. This would appear to be a further source of uncertainty in the modelled duration of each line of therapy. The total duration of each line of therapy, multiplied by the monthly utility value for that therapy has
then been used to generate a mean monthly utility value for patients who receive a second and subsequent lines of therapy. The three month utility value for these patients has then been calculated. Utility values for each line of therapy were pre-discounted to account for the fact that patients would receive different lines of therapy at different times, and the utility value is a mean average for one health state of receiving second and subsequent lines of therapy.

8.7 Healthcare resource utilisation and cost
8.7.1 Drug costs
British National Formulary (BNF) list prices have been used to cost all drugs. Degarelix treatment is costed as one 240mg injection in the first month followed by monthly injection of the 80mg dose, goserelin is costed as one 10.8mg injection every three months, and anti-androgen therapy with bicalutamide as one non-proprietary 50mg tablet daily starting three days before goserelin and continuing for three weeks after the first dose.

For patients who experience PSA failure on first-line hormone therapy, the costs second and subsequent line therapies are based on the expected response rates and durations of response. For chemotherapy, docetaxel at a dose of 75mg/m² every three weeks is assumed, with a patient body surface of 1.8m², and in combination with prednisolone 5mg twice daily. Premedication with dexamethasone 8mg given 12 hours, three hours and one hour before the docetaxel infusion is included, as per the docetaxel (Taxotere®) SPC. As with the utility values, the costs for second and subsequent lines of therapy were pre-discounted to account for the fact that patients would receive different lines of therapy at different times.

8.7.2 Treatment of adverse effects
The costs of adverse events are limited to the treatment of injection site reactions, which are assumed to involve five minutes of nursing time for the application of a cold compress. Published unit costs data are used to cost nursing time. It appears that these reactions are only modelled to occur during the first administration of degarelix 240mg, and not during any subsequent maintenance doses (see section 6.2).

8.7.3 Other health-related resource use and costs
All other health care resource use is reported to be based on company-sought expert opinion, and is costed using published Scottish and UK unit cost data. This includes the costs of hormone therapy reconstitution and administration by practice nurse, General Practitioner review appointments, PSA assessment and review with consultant urologist/oncologist during the first year of treatment, bone scans for half of those with PSA failure, oncologist visits for chemotherapy, etc. Palliative care is considered to involve multidisciplinary care and there are few data available to inform estimates specifically in prostate cancer. However, a mean cost of palliative care has been obtained from a study that described palliative care costs for several different types of cancer in 2000-2001, which has been inflated to 2007 prices.

Overall, practice is reported to vary and so the resource use that is modelled represents one scenario, but is applied equally to both treatment arms of the model.

8.8 Discounting
Costs and outcomes have been discounted at 3.5% per annum, which is the preferred discount rate. Rates of 0% - 6% have been explored in sensitivity analyses.
8.9 Results
8.9.1 Base case analysis
The incremental cost/QALY gained per patient for first-line treatment with degarelix compared with goserelin is estimated to be £11,496. This is based on incremental costs of £23,288 (£738,966 versus £715,678) and a gain of two QALYs (137.5 versus 135.5) with degarelix treatment, using a hypothetical cohort of 100 patients with metastatic prostate cancer.

The difference in costs and QALYs is primarily due to longer modelled treatment duration with degarelix as first-line therapy and during the second- and subsequent lines of therapy. There were no modelled gains in survival.

8.9.2 Sensitivity and scenario analyses
A wide range of one-way and two-way deterministic sensitivity analyses have been conducted to explore different assumptions around several parameters. These do not address the uncertainty regarding the duration of treatment and extrapolation in the longer term of the PSA response with degarelix and goserelin. Probabilistic sensitivity analysis has not been conducted, which is a limitation as the combined impact of uncertainty in several parameters is not fully explored.

In the one-way sensitivity analyses, all parameters used in the model have been varied within the range +/-25% of the base case value. The resultant tornado diagram indicates that the model was most sensitive to:

- the cost of the 80mg degarelix injection used in maintenance treatment (ICER ranges from being dominant over goserelin to £35,294/QALY gained),
- the assumed utility for distant symptomatic hormone-responsive disease (ICER ranges from £6,450/QALY gained to £52,725/QALY gained),
- the three month cost of goserelin (ICER ranges from £32,535 per QALY gained, to being dominant over goserelin).

Threshold analysis indicates that, individually and with all other parameters being equal to the base case scenario, the cost of the 80mg degarelix dose would need to increase by more than 7.4%, the cost of the goserelin three-month injection would need to decrease by more than 10.1% and the cumulative probability of PSA failure would need to increase by more than 16.0% for the ICER to exceed £20,000/QALY. The company asserts that there is no reason to expect that these scenarios would occur in practice.

Other parameters that resulted in ICERs greater than £20,000/QALY gained for degarelix compared with goserelin when values were explored within the range +/-25% were the cost of the degarelix in the first three months of treatment (ICER ranged £1,894 to £21,097 per QALY gained), and the probabilities of PSA failure at 12, 9 and 6 months with goserelin treatment (ICERs ranged between around £6,000 to around £24,000 per QALY gained). The influence of the probability of PSA failure at 3 months with goserelin is not presented in the tornado diagram of the top 20 most influential parameters on model outputs.

Two-way sensitivity analyses have been conducted to explore the impact of simultaneously varying the discount rate for costs and outcomes in the range 0% to 6%, and the impact of simultaneously varying the probability of injection site reactions with degarelix and goserelin within the range 0% to 100%. These analyses suggest that the model is insensitive to the assumed discount rates, and that the probability of injection site reactions with degarelix needs to be substantially greater than was observed in the study CS21 for the ICER to exceed £20,000/QALY gained. Given the uncertainty in other key parameters, these two-way sensitivity analyses are of limited value.
Six scenario analyses have been conducted. Only two of these significantly alter the model outputs from the base case analysis. When the probability of PSA failure with degarelix is assumed to be the same as with goserelin throughout the treatment period, degarelix is both more expensive and less effective than goserelin (i.e. degarelix is dominated). When the probability of PSA failure with degarelix and goserelin is as per the base case analysis in the first 12 months of treatment, but is assumed equal beyond 12 months of treatment, the ICER is £24,816 per QALY gained. This is a potentially important finding as there is some uncertainty in the extrapolation of PSA failure rates over the longer term. The approach to discounting costs and QALYs for the second and subsequent lines of therapy, the use of goserelin as monthly injections in the first three months of treatment, and the delivery of PSA results by the GP all had minimal impact on the base case ICER.

8.10 Review of published evidence on cost-effectiveness
Standard literature searches did not identify any published evidence on the cost-effectiveness of degarelix.

9.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

9.1 Description and critique of the company’s submission
The budget impact analysis relates to the use of degarelix in patients with metastatic prostate cancer. UK population estimates and prostate cancer prevalence are used to derive the number of patients with prostate cancer in Wales and Welsh Cancer Intelligence and Surveillance Unit (WCISU) data provide incidence data. It is assumed that the number of incident cases remains constant each year, and that degarelix will be used only in those newly diagnosed patients as switching patients who are already on LHRHa therapy is not considered to be feasible. It is assumed 90% of LHRHa therapy will be administered three-monthly, with the remaining 10% administered monthly, and that all will involve the use of anti-androgen therapy. Three scenarios of uptake are considered for metastatic prostate cancer patients: 50% of eligible LHRHa therapy replaced with degarelix; 100% of LHRHa therapy replaced with degarelix; and degarelix used only in those with specific symptoms of spinal cord compression, etc. There are a number of assumptions employed, which warrant caution in the interpretation of the budget impact estimates. These include the assumed constant treatment of patients with LHRHa or degarelix over the five years of treatment.

9.2 Perspective and time horizon
The budget impact analysis is conducted form the perspective of NHS Wales and considers a time horizon of five years.

9.3 Data sources
9.3.1 Incident and prevalent cases
Cancer statistics suggest that 215,000 men in the UK have prostate cancer. On the basis of UK and Wales population estimates, it is estimated that 0.75% of males in Wales had prostate cancer in 2001. Assuming a constant prevalence since 2001, and using mid-2007 population estimates, the company estimates that around 11,000 patients have prostate cancer in Wales.

Data from the British Association of Urological Surgeons cancer registry suggests that 8.5% of men with prostate cancer presented with metastatic disease in 2007. Applying this to the estimated 11,000 patients with prostate cancer in 2007 provides an estimate of 935 patients with prostate cancer in Wales.
WCISU data indicate that there were 2,552 new cases of prostate cancer in Wales in 2007\textsuperscript{21}. Assuming that the incidence of metastatic cancer is proportional to the incidence of all grades of prostate cancer, and on the basis of 8.5\% of cancers being metastatic at presentation, the number of new cases of metastatic cancer in 2007 is estimated as being 217\textsuperscript{2}.

Although the incidence of prostate cancer is increasing, this is primarily due to the increased awareness and screening (which would be expected to identify patients before they have metastatic disease). Therefore, it is simply assumed that the number of new cases of prostate cancer will be constant at 217 in each year\textsuperscript{2}. WCISU data from 1993 to 2002 is used to suggest that the average death rate was 5.4\%\textsuperscript{22}. This is assumed to remain constant each year\textsuperscript{2}. The net number of patients in each year is therefore estimated as 1102 in year 1 (which corresponds to 2007), rising to 1923 in year 5\textsuperscript{2}.

9.3.2 Projected rate of adoption and market share

It is assumed that all patients with metastatic prostate cancer would receive treatment and that only newly diagnosed patients with metastatic disease would receive treatment with degarelix, as switching of patients who are already using LHRHa is not considered to be feasible\textsuperscript{2}. On the basis of the above assumptions of a constant number of newly diagnosed patients with metastatic disease, it is anticipated that 217 patients would be eligible for treatment each year.

It is assumed that 10\% of patients would receive LHRHa therapy (goserelin, leuprorelin or triptorelin) as monthly injections and 90\% as three-monthly injections\textsuperscript{2}.

Three scenarios of uptake are presented as described in section 9.4. It is assumed in each of these that patients receive treatment continually and there no mortality until year 4, at which point 5\% of all patients die in each of years 4 and 5\textsuperscript{2}. The basis of this assumption is unclear and it should be noted that the base case analysis of the economic model permitted treatment with first-line hormone monotherapy for a maximum of 3 years (the actual mean duration of first-line monotherapy with degarelix and goserelin in the economic model was estimated to be 23.35 months and 19.67 months, respectively)\textsuperscript{2}. The overall duration of hormone therapy in the economic model, including combined therapy with other agents, is unclear.

9.3.3 Costs and resource use

The costs considered in the budget impact analysis are the drug acquisition costs for degarelix, the LHRHAS and for anti-androgen therapy for protection against early testosterone surge, and nursing time costs for administration. LHRHa drug costs are composed of the weighted average costs of goserelin, leuprorelin and triptorelin derived from company market research data on prescribing volumes (69.5\%, 16.6\% and 13.9\%, respectively)\textsuperscript{2}. Anti-androgen costs are based on a weighted mean average of non-proprietary bicalutamide, flutamide and cyproterone acetate derived from UK prescribing cost data. Administration costs are greater for degarelix than for LHRHa (based on 20 minutes of practice nurse time for degarelix, and 15 minutes for LHRHa) due to the need for reconstitution of degarelix\textsuperscript{2}.

9.4 Results

Three scenarios of uptake are considered in the budget impact analysis\textsuperscript{2}:

(i) 50\% of those newly diagnosed patients who would have been prescribed LHRHa are prescribed degarelix instead
(ii) 100\% of those newly diagnosed patients who would have been prescribed LHRHa are prescribed degarelix instead
(iii) Only patients with metastatic disease presenting with symptoms such as spinal cord compression, acute bladder outlet obstruction and painful bony metastases
are prescribed degarelix instead of LHRHa (assumed to be 43 patients each year, which is 20% of the 217 newly diagnosed patients with metastatic disease each year, the basis of which is unclear).

Table 1. Cumulative incremental cost of the use of degarelix compared with LHRHa therapy

<table>
<thead>
<tr>
<th>Scenario (i)</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>£74,190</td>
<td>£143,044</td>
<td>£211,898</td>
<td>£265,879</td>
<td>£331,014</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Scenario (ii)</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>£148,381</td>
<td>£286,088</td>
<td>£423,795</td>
<td>£531,758</td>
<td>£662,029</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Scenario (iii)</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>£29,687</td>
<td>£57,239</td>
<td>£84,790</td>
<td>£106,391</td>
<td>£132,455</td>
<td></td>
</tr>
</tbody>
</table>

These budget impact estimates should be interpreted with caution due to the range of assumptions employed in these scenarios.

9.5 Sensitivity analysis
No further sensitivity analyses have been conducted for the budget impact analysis.

9.6 Relevant comparator costs

Table 2. Example first year costs of first-line hormone therapy in metastatic prostate cancer

<table>
<thead>
<tr>
<th>Drug</th>
<th>Example SC dose</th>
<th>Annual cost £</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degarelix (Firmagon®)</td>
<td>240mg initially followed by 80mg monthly</td>
<td>£1,683.07</td>
</tr>
<tr>
<td>Goserelin (Zoladex LA®)*</td>
<td>10.8mg every three months</td>
<td>£1,069.92*</td>
</tr>
<tr>
<td>Leuprorelin (Prostap 3®)*</td>
<td>11.25mg every three months</td>
<td>£902.88</td>
</tr>
<tr>
<td>Triptorelin (Decapeptyl SR®)*</td>
<td>11.25mg every three months</td>
<td>£828.00*</td>
</tr>
</tbody>
</table>

*Excludes cost of initial anti-androgen therapy, which would be given for 3 days before LHRHa initiated and continued for three weeks. Anti-androgen costs would be £17.49 for usual dose of flutamide, £66.43 for usual dose of cyproterone acetate, or £98.50 for usual dose of bicalutamide (all non-proprietary).

10.0 ADDITIONAL INFORMATION

10.1 Guidance and audit requirements
The therapeutic effect of degarelix should be monitored by clinical parameters and PSA serum levels. In the case that the patient's clinical response appears to be sub-optimal, it should be confirmed that serum testosterone levels are remaining sufficiently suppressed. On the basis of company-sought expert opinion, it is assumed in the company submission that those patients who are to receive first line hormonal therapy will have degarelix and LHRHa administered by practice nurses. Shared care protocols for LHRHa have not been identified.

10.2 Related advice
interventional procedure guidelines related to the treatment of prostate cancer are also available on the NICE website.

- The European Association of Urology issued guidelines on the management of prostate cancer in 2008/9\textsuperscript{13,15}. These are generally aligned with the NICE guideline but provide a more detailed algorithm in terms of possible treatment options following first-line hormone therapy failure. However, the evidence base for this algorithm is unclear.
- The European Society for Medical Oncology issued clinical recommendations for the diagnosis, treatment and follow-up of patients in 2008\textsuperscript{24}.

10.3 Ongoing studies
Additional information was provided which remains commercial in confidence.

10.6 Patient organisation information
A patient organisation submission by the West Wales Prostate Cancer Support Group was provided to members.

10.7 Medical expert / Clinical expert summary
Medical expert views were provided to members.
GLOSSARY

Gleason score:
An internationally recognised grading system, based on examination of tissue obtained by prostate biopsy, where a pathologist allocates an overall cell abnormality score that can help predict prostate tumour behaviour. A low Gleason score (≤6) indicates a relatively favourable cancer, a high Gleason score (≥8) indicates a relatively aggressive cancer⁴.

Incidence:
The rate at which new cases occur in a population during a specified period²⁵.

Prevalence:
The proportion of a population that are cases at a point in time²⁵.

Prostate Specific Antigen (PSA):
A protein produced by the prostate gland and identified in the blood. Men with prostate cancer tend to have higher levels of PSA in their blood (although most men with prostate cancer have normal PSA levels). PSA levels may also be increased by conditions other than cancer and levels tend to increase naturally with age⁴.
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    2009.
    therapies in advanced prostate cancer Journal of the National Cancer Institute.


Appendix 1. Additional Clinical Information

Table 1A. Pivotal phase III trial of degarelix versus leuprorelin

<table>
<thead>
<tr>
<th>Ref</th>
<th>Study type</th>
<th>No. of patients</th>
<th>Inclusion and exclusion criteria</th>
<th>Baseline characteristics</th>
<th>Treatment regimen</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Study CS21,10 | Phase III, open-label, non-inferiority, comparative trial | 620 patients randomised | **Inclusion criteria:**
- Confirmed prostate carcinoma of any stage
- Age >18 years
- Serum testosterone >1.5 ng/mL
- PSA >2ng/mL
- ECOG PS ≤2
- Life expectancy >12 months
- Not considered for curative treatment

**Exclusion criteria:**
- Previous or concurrent hormonal management of prostate cancer - surgical or medicinal (apart from neoadjuvant/adjuvant hormonal therapy for a maximum of 6 months and terminated at least 6 months before inclusion)
- Concurrent treatment with a 5α-reductase inhibitor
- History of risk factors for QT/QTcF interval prolongation
- Patients receiving medicines that may prolong QT/QTcF interval

<table>
<thead>
<tr>
<th>Of the wholeITT population:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age: 74yrs</td>
</tr>
<tr>
<td>Race: Caucasian 87%</td>
</tr>
<tr>
<td>Prostate cancer stage:</td>
</tr>
<tr>
<td>Localised: 31%</td>
</tr>
<tr>
<td>locally advanced: 29%</td>
</tr>
<tr>
<td>metastatic: 20%</td>
</tr>
<tr>
<td>unknown metastatic status:  7%</td>
</tr>
<tr>
<td>previous curative intent surgery or radiation and a rising PSA: 13%</td>
</tr>
</tbody>
</table>

**PSA mean levels ng/mL:**
- Degarelix 240/80: 112
- Degarelix 240/160: 268
- Leuprorelin: 218

**Gleason score:**
- 2-4: 11%
- 5-6: 33%
- 7-10: 57%

Degarelix 240mg SC initially followed by 80mg SC monthly (n=207) versus Leuprorelin 7.5mg IM monthly (n=201)

*(NB: anti-androgen received by 23 patients treated with leuprorelin and 4 patients treated with degarelix – mostly treatment emergent use)*

**Primary endpoint:**
Probability of achieving and maintaining testosterone levels <0.5ng/mL between Day 28 and Day 364 (ITT analysis):
- Degarelix 240/80: 97.2% (95% CI: 93.5 to 98.8)
- Leuprorelin: 96.4% (95% CI: 92.5 to 98.2)

Difference 0.875% (97.5% CI: -3.21 to 4.96)

Pre-specified criterion for non-inferiority of degarelix to leuprorelin achieved.

**Selected secondary / other endpoints (degarelix 240/80 versus leuprorelin):**
- % patients with testosterone surge* in first 2 weeks: 0% vs. 80.1%; p<0.0001
- % patients with testosterone level ≤0.5 ng/mL at Day 3: 96.1% vs. 0%; p<0.0001
- % change (median) in PSA from baseline to Day 14: -63.4% vs. -17.9%; p<0.0001
- Day 28: -84.9% vs. -66.7%; p<0.0001
- Day 56 to 364: no significant difference
- % patients with PSA failure†: 8% versus 13%

Probability of completing the study without PSA failure*:
- Degarelix 240/80: 91.1% (95% CI: 85.9 to 94.5)
- Leuprorelin: 85.9% (95% CI: 79.9 to 90.2)

Serum luteinising hormone and follicle stimulating hormone levels followed a similar time profile to testosterone.

ECOG PS = ECOG performance status; IM = intramuscular; ng = nanograms; PSA = Prostate specific antigen; SC = subcutaneous; *testosterone surge = testosterone level exceeded baseline by ≥15% on any two days during the first two weeks of treatment; †PSA failure = two consecutive increases of 50%, and at least 5 nanograms/mL, as compared to nadir.

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All Wales Medicines Strategy Group Final Appraisal Report
Degarelix (Firmagon®) – December 2009