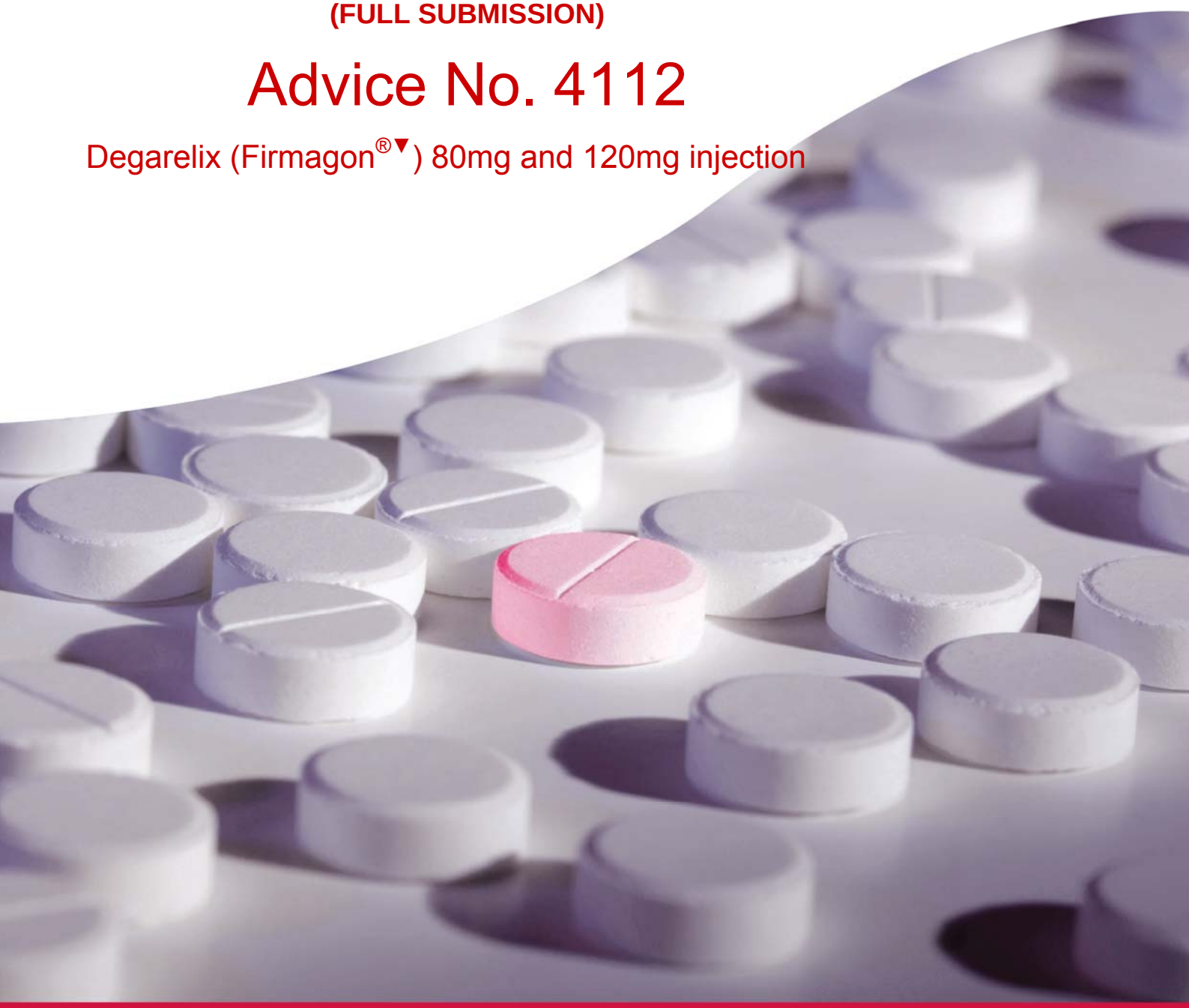
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(FULL SUBMISSION)

Advice No. 4112

Degarelix (Firmagon®▼) 80mg and 120mg injection



In collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University

AWMSG Secretariat Assessment Report – Advice No. 4112
Degarelix (Firmagon®) 80 mg and 120 mg injection

This assessment report is based on evidence submitted by Ferring Pharmaceuticals (UK) on 6 July 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Degarelix (Firmagon®) is a gonadotrophin releasing hormone (GnRH) antagonist indicated for treatment of adult male patients with advanced hormone-dependent prostate cancer[2,3].
Dosing	Degarelix is administered as a subcutaneous injection in the abdominal region. The starting dose of degarelix should be 240 mg, administered as two 120 mg injections, following by a monthly maintenance dose of 80 mg. The first maintenance dose should be given one month after the starting dose[2,3].
Marketing authorisation date	17 February 2009[2,3].
UK launch date	5 May 2009[1].

2.0 DECISION CONTEXT

2.1 Background

Prostate cancer is the most common cancer affecting men in Wales, with a prevalence of 1%[4]; 2,437 cases were reported in Wales during 2010, accounting for approximately 26% of newly diagnosed cancers in men[5]. Wales has the highest incidence of prostate cancer in the UK, but mortality rates are very similar to those for the whole of the UK (24.0 and 24.1 per 100,000 population in Wales and the UK respectively)[6].

The responsiveness of prostate cancer to androgen deprivation is well documented and this has become a mainstay of advanced prostate cancer management, achieved by surgical/medical castration or by blockade of the androgen receptor[7]. Long-acting luteinising hormone-releasing hormone (LHRH; also known as gonadotrophin-releasing hormone [GnRH]) agonists, such as goserelin, leuprorelin and triptorelin, suppress testosterone production to castration levels (50 nanograms/dl) within 2–3 weeks of treatment initiation. However, LHRH agonist treatment causes an initial increase in testosterone, known as a surge, which can lead to a flare in clinical symptoms. Current European guidelines recommend that patients initially receive concomitant therapy with an anti-androgen treatment to decrease incidence of clinical flare[7,8].

Degarelix is a GnRH antagonist that competitively binds to the GnRH receptors in the pituitary gland, reducing the release of the gonadotrophins, luteinising hormone and follicle stimulating hormone, causing diminished secretion of testosterone[2,3]. In contrast with LHRH agonists, degarelix and other GnRH antagonists do not induce a testosterone surge with potential symptomatic flare after the initiation of treatment[2,3].

2.2 Comparators

The comparators requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) were goserelin, leuprorelin and triptorelin, administered in combination with initial anti-androgen therapy to avoid clinical flare.

2.3 Guidance and related advice

- European Association of Urology (EAU). Guidelines on prostate cancer (2012)[7].
- European Society for Medical Oncology (ESMO). Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2010)[8].
- National Institute for Health and Clinical Excellence (NICE). Clinical Guidelines 58. Prostate cancer: diagnosis and treatment (2008)[9].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes the pivotal phase III study CS21 comparing the effectiveness of degarelix and leuprorelin in prostate cancer patients, along with the extension study CS21A[1]. The submission also includes a phase III study comparing degarelix and goserelin, a literature review evaluating the comparative efficacy of goserelin, leuprorelin and triptorelin and five phase II studies. The phase II studies will not be discussed further; all were dose-finding or safety studies with no active comparator arm and therefore do not contribute any substantial evidence of comparative effectiveness beyond that provided by the phase III studies.

3.1 Comparative efficacy

3.1.1 Study CS21

This randomised, active-controlled, open-label, multi-centre, twelve-month, phase III study evaluated the safety and efficacy of degarelix versus leuprorelin for maintaining testosterone suppression in prostate cancer patients[10]. Patients (n = 610) were randomised (1:1:1) to one of three treatment arms. There were two degarelix treatment groups; each received an initial degarelix subcutaneous injection of 240 mg, followed by monthly maintenance doses of either 80 mg or 160 mg[10]. The licensed maintenance dose of degarelix is 80 mg[2,3] and therefore results from the 80 mg treatment group are most relevant; the 160 mg maintenance dose is not discussed further. Patients in the third treatment group received leuprorelin (7.5 mg as a single monthly intramuscular injection) and could also receive the anti-androgen bicalutamide (50 mg tablet once daily) during treatment initiation to prevent clinical flare at the discretion of the investigator [10].

Subjects entering the study were males (≥ 18 years) with adenocarcinoma of the prostate where endocrine treatment (except neoadjuvant therapy) was indicated, a serum testosterone level of > 1.5 nanograms/ml, a prostate-specific antigen (PSA) level of ≥ 2 nanograms/ml, an Eastern Cooperative Oncology Group score of ≤ 2 (see Glossary for definition) and a life expectancy ≥ 12 months. Main exclusion criteria were any previous or current hormonal treatment for prostate cancer, apart from neoadjuvant/adjuvant therapy (≤ six months duration) that ended at least six months before study inclusion. Patients considered to be candidates for curative therapy were also excluded[10].

The primary endpoint was testosterone response rate, defined as a testosterone level ≤ 0.5 nanograms/ml from day 28 and 364. Secondary endpoints included the

proportion of patients with testosterone surge during the first two weeks of treatment (defined as testosterone levels exceeding baseline by ≥ 15% on any two days during the first two weeks of treatment), quality-of-life outcomes and percentage change in PSA from baseline to day 14 and day 28[10].

Results for the primary endpoint and other key outcomes are presented in Table 1. The testosterone response rate in the ITT population was 97.2% in the degarelix group and 96.4% in leuprorelin-treated patients[10]. The difference between treatment arms was 0.88% (97.5% confidence interval [CI]: -3.21 to 4.96), which fulfilled the pre-specified criterion for demonstration of non-inferiority of degarelix to leuprorelin (the lower limit of the 97.5% CI being greater than -10%)[11]. Reduction of PSA levels from baseline at day 14 and 28 was significantly greater in degarelix-treated patients than the leuprorelin group; however, PSA level reduction in the small subgroup of patients receiving leuprorelin with bicalutamide (n = 23) were similar to those in degarelix-treated patients[10]. A post hoc analysis additionally demonstrated that patients receiving degarelix had a lower risk of PSA recurrence/failure (defined as PSA increase ≥ 50% from nadir and ≥ 5 nanograms/ml on two consecutive occasions at least two weeks apart) or death compared with leuprorelin (p = 0.0495)[12]. Quality-of-life outcomes were comparable between the groups[13].

Table 1. Results for key endpoints from Study CS21 (ITT population)[10–12].

Endpoints	Degarelix (n = 207)	Leuprorelin (n = 201)
Primary endpoint		
Testosterone response rate*	202 (97.2%) (95% CI: 93.5, 98.8)	194 (96.4%) (95% CI: 92.5, 98.2)
Secondary endpoints		
Patients with testosterone surge during the first two weeks of treatment	0 (0%)	161 (80.1%)
Percentage change in PSA from baseline to day 14	-63.4%	-17.9%
Percentage change in PSA from baseline to day 28	-84.9%	-66.7%
Post hoc analyses		
Probability of no PSA failure by day 364	91.1%	85.9%
Probability of survival by day 364	97.4%	95.1%
*cumulative probability of a testosterone level ≤ 0.5 nanograms/ml from day 28 and 364., estimated by the Kaplan-Meier method.		

3.1.2 CS21A extension study

Patients who completed study CS21 were eligible to enter this extension study and either continued on the same monthly degarelix maintenance dose (80 mg monthly dose: n = 125; 160 mg monthly dose n = 126), or, if they had received leuprorelin were re-randomised to receive a degarelix dose of 160 mg (n = 66) or 80 mg (n = 69); all patients were later switched to receive 80 mg following marketing authorisation[14]. Although the study primary endpoints were safety analyses, efficacy data were collected as secondary endpoints. Kaplan-Meier estimates of the probabilities of the testosterone response rate (levels ≤ 0.5 nanograms/ml) over five years were 82.0% and 84.1% for the degarelix 80 mg and leuprorelin/degarelix 80 mg groups, respectively[15].

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3.1.3 Comparison of degarelix with goserelin

This was a randomised, parallel-arm, active-controlled, open-label, phase III study in 182 prostate cancer patients who received degarelix (starting dose 240 mg and monthly maintenance dose of 80 mg) or goserelin (3.6 mg implants inserted monthly with 50 mg bicalutamide daily for initial 28 days of treatment) for 12 weeks[16].

The primary efficacy endpoint was mean percentage change in total prostate volume; this was similar between the treatment groups (−37.2% in the degarelix group versus −39.0% in goserelin-treated patients) and met the predefined non-inferiority criterion. This was supported by secondary endpoints, including decreased International Prostate Symptom Score (see Glossary for explanation of scoring system) and testosterone suppression; PSA level decreases from baseline were also similar between the two arms[16].

3.1.4 Comparison of degarelix with goserelin, leuprorelin and triptorelin

The company submission also includes a literature review, conducted with the aim of identifying evidence to support the application of outcomes from the CS21 study to other therapies used in clinical practice, including three-monthly goserelin, which the company suggests is the most widely used therapy in Welsh patients[1]. From the literature review the company conclude that there is little evidence of difference in outcomes during comparisons of leuprorelin 7.5 mg monthly versus 3.75 mg monthly, leuprorelin versus goserelin or triptorelin and monthly LHRH agonist injections versus a three-monthly dose[1].

3.2 Comparative safety

Safety evidence is provided by study CS21, the extension study CS21A and the comparison of degarelix and goserelin[1].

The overall incidence of adverse events (AEs) during study CS21 was comparable between the degarelix (80 mg maintenance dose regimen) and leuprorelin groups (163/207 [79%] versus 156/201 [78%] respectively), as was the incidence of serious AEs (21 [10%] versus 28 [14%])[10]. Discontinuations due to AEs occurred in 15 (7%) degarelix-treated patients and 12 (6%) in the leuprorelin group. A total of five and nine deaths occurred in each treatment group respectively, none of which were considered related to treatment. Degarelix treatment was associated with higher incidences of injection site reaction (35% versus <1% in the leuprorelin group)[10].

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When treatment-related injection site reactions were excluded, the incidence of remaining AEs were comparable[11].

The most frequently reported AE was flushing (26% degarelix versus 21% leuprorelin). Additionally, more degarelix-treated patients reported chills (3% versus none), while more patients in the leuprorelin group reported arthralgia (5% versus 9%) and urinary tract infections (5% versus 9%)[10]. Cardiovascular side effects were reported by 9% and 13% in patients receiving degarelix (combined 80 mg and 160 mg dose treatment groups) and leuprorelin, respectively[10].

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Treatment-emergent AEs were reported by 39% and 48% of patients receiving degarelix and goserelin respectively, of which 2% and 11% were considered severe, while 35% in each group were considered treatment-related[16]. Most adverse drug reactions reported were injection site reactions, which were reported only in the

degarelix group; these were predominantly pain (14%), erythema (4%) and swelling (4%)[16].

3.3 AWTTC critique

- The comparators requested by AWTTC were leuprorelin, goserelin and triptorelin. The company submission includes studies comparing the effectiveness of degarelix with that of leuprorelin and goserelin[1]. A systematic review has been undertaken to identify evidence to support the application of outcomes from the CS21 study to commonly used LHRH agonist therapies, and the company concludes that there is little evidence of differences in effects between the regimens.
- The non-inferiority of degarelix in comparison with leuprorelin and goserelin was demonstrated in terms of surrogate primary endpoints of testosterone suppression and reduction in total prostate volume, respectively[10,16]. Clinical improvement in terms of survival or tumour reduction has not been explored as part of a pre-defined endpoint[10,16]. However, post-hoc analysis of progression-free and overall survival from study CS21/CS21A suggests that there could also be a beneficial effect with degarelix treatment in terms of these outcomes[10,14].
- Secondary endpoint data from study CS21 indicate that degarelix treatment leads to more rapid suppression of testosterone levels than leuprorelin and is not associated with an initial surge in testosterone levels[11]. At the time of licensing, CHMP noted that the major clinical added value of this product was avoidance of testosterone flare (without the need for concomitant anti-androgen treatment) and suggests that degarelix is especially useful when a rapid reduction in testosterone levels is of critical importance[11]. Current EAU guidelines state that in patients with impending spinal cord compression, strategies for immediate ablation of testosterone levels, such as surgical castration or GnRH antagonist use, should be employed[7]. EAU guidelines also recommend that where a depot LHRH agonist is used, anti-androgen treatment should be initiated concurrently[7]. During study CS21, anti-androgen treatment (bicalutamide) was administered to only 11% of patients receiving leuprorelin. It should be noted that in this subgroup, incidence of testosterone surge during the first two weeks of treatment was lower than in patients receiving leuprorelin only[10]. Furthermore, in the patients receiving leuprorelin plus bicalutamide, PSA reduction was more rapid than in those who only received leuprorelin, and was comparable to that of degarelix-treated patients. Beyond 28 days, there was no significant difference in the degree of testosterone suppression with degarelix and leuprorelin[10]. Therefore it remains unclear whether degarelix offers any clinical benefit in terms of avoidance of testosterone flare over an LHRH agonist, provided an anti-androgen is given concomitantly, as is standard practice in Wales.
- The leuprorelin 7.5 mg dose administered during study CS21/CS21A is currently unlicensed in the UK[17,18]. Further, the company acknowledge that the submitted clinical studies do not utilise the comparator dosing regimen that are most commonly prescribed in Wales, which is suggested to be goserelin three-monthly injections[1].
- The submitted clinical studies enrolled patients with prostate cancer, including localised and non-classifiable disease[1]. Marketing authorisation was subsequently granted for use in patients with advanced prostate cancer[2,3], which encompasses only 50% of the pivotal study population[10].
- The incidence of injection site reactions in degarelix-treated patients was high in both clinical studies submitted[1]. This led to treatment discontinuation in one patient during study CS21[19]. (Commercial in confidence material removed).

- Degarelix is administered monthly by subcutaneous injection and requires reconstitution before injection[2,3]. By contrast, the LHRH agonist comparators are available in formulations that can be administered less frequently (every 3–6 months) and do not require reconstitution[17,20,21].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost utility analysis of degarelix, administered once monthly, for the treatment of advanced hormone-dependent prostate cancer[1]. A subgroup analysis in patients considered to be at higher risk of progression, defined by a PSA level > 20 nanograms/ml, is also provided. The primary comparator considered is leuprorelin, administered at its licensed dose of 11.25 mg once every three months, with bicalutamide (50 mg daily for four weeks) for testosterone surge protection. Alternative LHRH agonists are also considered as comparators (leuprorelin 3.75 mg administered monthly, and goserelin and triptorelin administered monthly or three-monthly at licensed doses).

The analysis is based on a semi-Markov model structure consisting of three states: prostate cancer first line treatment; prostate cancer second line and subsequent line treatment; and death. Following first line treatment with either degarelix or one of the comparators, second line and subsequent line treatment consists of follow-on hormonal therapy, followed by chemotherapy with docetaxel, followed by abiraterone, and then palliative care. The model time horizon is 20 years in the base case, taken to represent a life-time horizon for a cohort with a starting age of 72 years.

Movement from the first to the second line treatment state over the whole time horizon is driven by the one-year PSA recurrence rates observed in study CS21. The efficacy of all secondary LHRH agonist comparators is assumed equal to that of leuprorelin, based on a literature review reporting little difference in their efficacies[22]. Movement between the second and subsequent treatments is based on treatment durations indicated in EAU 2010 guidelines[23]. In the reported absence of recent Welsh prostate cancer-specific mortality rates, Scottish mortality data are assumed, with adjustment of survival extension associated with abiraterone use based on NICE Technology Appraisal guidance[24]. AEs from LHRH agonist testosterone surge, spinal cord compression and musculoskeletal events are not included in the base case model but are examined in a sensitivity analysis. Utility values applied in the model are derived from the literature[25] and the AWMSG Secretariat Assessment Report for abiraterone[26]. Resource use data are obtained from the literature and expert opinion. Degarelix acquisition costs are based on a confidential price agreed with Patient Access Scheme Wales Group (PASWG).

4.1.2 Results

Table 2. Company-reported results of the base case analysis.

	Whole advanced hormone-dependent prostate cancer population			Subgroup with PSA > 20 nanograms/ml		
	Degarelix	**Leuprorelin**	**Difference**	**Degarelix**	**Leuprorelin**	**Difference**
Drug cost – 1st-line hormonal treatment	£3,904	£2,616	£1,288	£3,132	£1,875	£1,257
Drug cost – 2nd-line hormonal treatments	£224	£282	-£58	£320	£373	-£52
Drug cost – non-hormonal treatment	£8,431	£11,833	-£3,402	£11,974	£15,562	-£3,587
Cost of staff time and tests – 1st-line hormonal treatment	£1,424	£627	£797	£1,198	£541	£657
Cost of staff time and tests – 2nd-line hormonal treatment	£338	£387	-£50	£482	£511	-£29
Cost of staff time and tests – non-hormonal treatment	£1,785	£2,525	-£739	£2,559	£3,354	-£794
Cost of palliative care	£3,183	£4,652	-£1,470	£4,775	£6,536	-£1,761
Total cost per patient	£19,289	£22,922	-£3,633	£24,441	£28,751	-£4,310
Total LYG per patient	4.73	4.74	-0.01	4.74	4.74	0.00
Total QALYs per patient	3.79	3.58	0.20	3.57	3.33	0.24
ICER (£/QALY gained)	**Degarelix dominates leuprorelin***			**Degarelix dominates leuprorelin***		

*Degarelix is estimated to be both more effective and less costly than leuprorelin.
LYG: life-year gained; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year.

The model estimates first-line degarelix treatment to generate more quality-adjusted life-years (QALYs) at lower overall costs than the comparator in both the whole advanced hormone-dependent prostate cancer population and the subgroup with baseline PSA > 20 nanograms/ml. The results are driven by the modelled difference in PSA recurrence rates, which lead to patients on degarelix treatment remaining in the first-line treatment state, with the highest quality of life, for longer, and patients on leuprorelin treatment progressing more quickly onto more costly second- and subsequent-line treatments, with lower quality of life.

Probabilistic sensitivity analyses suggest the probability of degarelix being cost-effective is over 94% at a threshold of £20,000 per QALY gained, with the vast majority of simulations indicating dominance over leuprorelin. A wide range of scenario and one-way sensitivity analyses were undertaken. The results show that the model is most sensitive to the assumed hazard ratio (HR) for PSA recurrence (1.71 [95% CI 1.00 to 2.93] for the whole population; 1.74 [95% CI 0.99 to 3.07] for the subgroup with PSA > 20 nanograms/ml). Threshold analyses showed that the incremental cost-effectiveness ratios (ICERs) exceeded £30,000 per QALY gained at HRs (applied for the 20-year time horizon) of 1.08 and 1.06 for the whole population and the subgroup, respectively. Assuming no difference in outcomes resulted in degarelix being more costly by £1,300 to £1,400. Assuming the base case HRs applied only for the first year

of treatment, and equal treatment effectiveness thereafter, degarelix remained dominant over leuprorelin whenever abiraterone was included in the subsequent lines of treatment; exclusion of abiraterone resulted in an ICER of £7,000 per QALY gained for the whole population and dominance over leuprorelin in the subgroup with PSA > 20 nanograms/ml. Degarelix maintained its dominance over leuprorelin in all other scenario and sensitivity analyses reported. Assuming the lower costs of alternative LHRH agonists in the base case model, degarelix remained dominant.

4.1.3 AWTTC critique

It is not certain that the base case analyses provided by the company represent the most plausible estimates of the cost-effectiveness of degarelix in practice. The model is driven by, and very sensitive to, the HRs for PSA recurrence. PSA recurrence was a secondary surrogate endpoint, observed at one-year follow-up in the pivotal CS21 trial in which the comparator does not reflect current treatment in practice. Confidence intervals around these HRs are very wide, reflecting considerable uncertainty, and the HRs are applied for the full 20-year time horizon, which assumes ongoing benefit for degarelix. PSA recurrence only occurred by one year in the small subgroup of patients with baseline PSA values > 20 nanograms/ml, and results in that subgroup are based on a post hoc analysis. However, in extensive sensitivity and scenario analyses, many modelled estimates consistently fell within conventional thresholds for cost-effectiveness, in the context of the price agreed with PASWG.

Strengths of the economic evidence include:

- A pragmatic approach has been adopted to modelling the treatment pathway and efficacy of second and subsequent lines of therapy.
- A wide range of sensitivity and scenario analyses have been conducted to explore the impact of key assumptions.

Limitations of the economic evidence include:

- It is assumed that the outcomes for patients in the CS21 trial are representative of outcomes with all LHRH agonists, including goserelin 10.8 mg administered three-monthly in combination with an anti-androgen, which is often used as a first-line treatment in Wales. Results of literature reviews have been provided to support the assumptions of clinical equivalence among all the LHRH agonists and the doses used, but the company acknowledge that the available sources of evidence are of moderate to poor quality.
- A scenario of equal efficacy between degarelix and leuprorelin may be plausible based on the uncertainty surrounding the HRs for PSA recurrence. In such a scenario, degarelix would be associated with additional costs of £1,300 to £1,400 per patient and little/no difference in outcomes over the modelled lifetime using the base case model parameters for extrapolation over the long-term.
- The utility values and resource use data assumed in the model appear subject to uncertainty, being based on limited literature and expert opinion. The model results were sensitive to changes in the assumed utility values, which appear to exceed population norms; however, for all values examined in the sensitivity analysis degarelix remained cost-effective at the £20,000 per QALY threshold.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have identified two published studies of the cost-effectiveness of degarelix within its current licensed indication.

The first study is an abstract/poster presentation of the economic evidence resubmitted to the Scottish Medicines Consortium by the company. In that submission, goserelin

was the primary comparator, and the model structure and assumptions are similar to those of the model submitted by the company to AWMSG; however, abiraterone was not available as a subsequent line of therapy at the time of the study. The authors conclude degarelix is dominant over goserelin[27].

The second study is a published cost utility analysis of degarelix compared against triptorelin plus short-term anti-androgen treatment in the management of patients with metastatic prostate cancer[28], which was originally conducted to inform local decision-making in South-West England[29]. The model consisted of a decision tree monitoring a hypothetical cohort of patients aged 70 years from the start of hormonal treatment to the end of the first month, and a Markov model monitoring patients from the end of month one for a time horizon of 10 years. In the base case analysis, the ICER for degarelix compared to triptorelin plus anti-androgen treatment was £59,000 per QALY gained. The ICER was very sensitive to the price of degarelix, and if the price was reduced to 70% of the market price, degarelix became dominant over triptorelin plus anti-androgen treatment, i.e. it costs less and produces more QALYs[28,29].

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company submission reports that 2,437 new patients were diagnosed with prostate cancer in Wales in 2010[1]. Based on 2006–2010 incidence data, an annual increase rate of 2.6% has been estimated. Hence, the number of newly diagnosed cases has been estimated to be 2,565 in 2012 rising to 2,834 in 2016. Using pack sales for the currently prescribed LHRH agonists for two years up to December 2011 and assumptions regarding the proportion of patients taking these agonists for prostate cancer, the number of males receiving LHRH agonists for prostate cancers has been estimated to be 3,674 in 2011. Applying the above annual incidence of 2.6%, 3,770 patients are estimated to be treated with LHRH agonists in 2012, rising to 4,178 in 2016. The company reports that only incident (newly diagnosed) cases will be eligible to receive degarelix and to be maintained on it after that. The company estimates that, in 2012, 838 patients will be eligible for treatment with degarelix, rising to a cumulative total of 2,864 patients eligible for degarelix treatment in 2016. However, the estimated market share of degarelix, based on the company sales projections, is (commercial in confidence material removed). Using these estimates, the number of patients expected to receive degarelix is calculated to be (commercial in confidence material removed).

5.1.2 Results

The company used the cost-effectiveness model to calculate the total annual cost of degarelix and leuprorelin acetate three-monthly treatment for each of the next five years. The results showed that the total cumulative per patient annual costs of using degarelix is estimated to be £2,109 in 2012 rising to £13,182 in 2016. Cumulative per patient annual costs of treatment with leuprorelin instead would be £1,874 in 2012 rising to £15,898 in 2016. Hence, a net cost is expected from using degarelix in years 2012 and 2013 and a cost saving from 2014 onwards. Supplementary analyses have been provided by the company in which degarelix replaces alternative LHRA agonists. The results are detailed in the table below.

Table 3. Company-reported costs associated with use of degarelix for the treatment of advanced prostate cancer.

	Year 1 (2012)	Year 2 (2013)	Year 3 (2014)	Year 4 (2015)	Year 5 (2016)
Number of eligible patients	838	1,506	2,044	2,484	2,846
Uptake (%)	(commercial in confidence material removed)				
Treated patients					
Net costs per patient vs. leuprorelin acetate three-monthly					
Administration and monitoring	£8,743	£18,711	£28,826	£39,550	£53,714
Primary care	£7,430	£19,576	£31,722	£45,113	£62,265
Secondary & tertiary care	-£5,363	-£21,318	-£65,847	-£115,773	-£165,477
Staffing	0	0	0	0	0
Infrastructure	0	0	0	0	0
Personal social services	0	0	0	0	0
Overall net cost vs. leuprorelin acetate three-monthly	£10,810	£16,970	-£5,299	-£31,111	-£49,498
Net costs per patient vs. alternative LHRH agonists					
Overall net cost vs. Goserelin three-monthly	£9,108	£16,037	–£7,122	–£33,824	–£53,149
Overall net cost vs. Goserelin once monthly	£7,334	–£22,250	–£58,826	–£100,017	–£142,573
Overall net cost vs. Leuprorelin acetate once monthly	£1,970	–£25,190	–£64,568	–£108,566	–£154,075
Overall net cost vs. Triptoreline three-monthly	£13,997	£18,716	-£1,888	–£26,033	–£42,666
Overall net cost vs. Triptoreline once monthly	£5,239	-£23,398	–£61,069	–£103,356	–£147,066

5.1.3 AWTTC critique of the budget impact analysis

- The estimated number of incident cases of prostate cancer in Wales in 2011 was calculated based on LHRH agonist pack sales and assumptions regarding the proportion of patients receiving these treatments for prostate cancer. These estimates are subject to uncertainty.
- The anticipated market uptake is a key component of the estimated budget impact and is inevitably a source of uncertainty.
- The budget impact anticipated is derived from the economic model, using the Wales Patient Access Scheme (WPAS) agreed price for degarelix. The limitations and uncertainties in the main cost drivers in the economic model also apply to the budget impact estimates.
- Given the aforementioned limitations, there appears to be considerable uncertainty in the budget impact estimates provided by the company.

5.2 Comparative unit costs

Table 4 provides examples of costs for degarelix and comparator treatments for advanced prostate cancer. LHRH agonists are initially to be given in combination with an anti-androgen for testosterone flare protection.

Table 4. Examples of annual costs for treatment of prostate cancer.

Drug	Example regimen	Approximate annual cost
Degarelix (Firmagon®) injection 80 mg and 120 mg vials	Initially two 120 mg by subcutaneous injection, then 80 mg every month.	£1,683 in first year £1,552 subsequent years (full list price)*
LHRH agonists		
Leuprorelin (Prostap®) injection 3.75 mg vial	One injection monthly	£903
Leuprorelin (Prostap®) injection 11.25 mg vial	One injection every three months	£903
Goserelin (Novgos®) implant 3.6 mg prefilled syringe	One implant every 28 days	£763
Goserelin (Zoladex®) implant 3.6 mg in syringe applicator	One implant every 28 days	£848
Goserelin (Zoladex® LA) implant 10.8 mg in syringe applicator	One implant every 12 weeks	£1,018
Triptorelin (Decapeptyl® SR) injection 3mg vial	One injection every four weeks	£897
Triptorelin (Decapeptyl® SR) injection 11.25 mg vial	One injection every three months	£828
Triptorelin (Decapeptyl® SR) injection 22.5 mg vial	One injection every six months	£828
Triptorelin (Gonapeptyl® Depot) 3.75 mg injection	One injection every four weeks	£1,062
Gonadorelin analogues		
Histrelin (Vantas®) 50 mg implant	One implant every 12 months	£ 990
Buserelin (Superfact®) Injection 1 mg/ml Intranasal spray 100 microgram per metered spray	500 microgram injection every eight hours for seven days Then one intranasal spray into each nostril six times daily	£1,116
Short-term anti-androgens for testosterone flare protection with LHRH agonists		
Bicalutamide (non-proprietary) tablets, 50 mg	50 mg once daily started at least three days before gonadorelin therapy	£4†
Cyproterone (non-proprietary) Tablets, 50 and 100 mg	100 mg twice daily for 7 days before initiation of gonadorelin analogue, followed by 100 mg twice daily for 3–4 weeks	£51–£77
Flutamide (non-proprietary) tablets, 250 mg	250 mg three times daily	£38†

* Cost of degarelix is based on the full list price. A confidential price of degarelix in Wales has been agreed via PASWG.
Other drug costs are based on BNF 63 and MIMS list prices as of 1 August 2012[30,31].
† Cost based on a total course of four weeks
This table does not imply therapeutic equivalence of the stated drugs and doses.
See all relevant SPCs for full dosing details[2,3,17,18,20,21,32–42].

6.0 ADDITIONAL INFORMATION

6.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, degarelix (Firmagon®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

6.2 Ongoing studies

The company submission highlighted several ongoing studies that are likely to be available within 6–12 months, including one phase I study (CS38), one phase II study

(CS27), six phase III studies (CS29, CS30, CS34, CS42, CS42A and CS43) and three non-interventional studies in prostate cancer patients (CS39, CS41 and CS46)[1]. These studies are unlikely to provide further data that could inform the comparison of degarelix with LHRH agonists for the treatment of advanced hormone-dependent prostate cancer in Welsh patients.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search

Date of evidence search: 24 July 2012
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Eastern Cooperative Oncology Group (ECOG) performance status score
A scale from 0 to 5, where: 0 indicates that the patient is fully active and able to undertake all pre-disease activities without restriction; 1 indicates the patient is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; 2 indicates that the patient is ambulatory and up and about more than 50% of waking hours and is capable of all self-care but unable to carry out any work activities[43].

International Prostate Symptom Score (IPSS)
This scoring system is used in the assessment of lower urinary tract symptoms in men[44].

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