Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

degarelix 120mg and 80mg powder and solvent for solution for injection (Firmagon®)

SMC No. (560/09)

Ferring Pharmaceuticals Ltd

17 December 2010

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

degarelix (Firmagon®) is accepted for use within NHS Scotland.

Indication under review: degarelix is a gonadotropin-releasing hormone (GnRH) antagonist indicated for the treatment of adult male patients with advanced hormone-dependent prostate cancer.

In one study that included patients with all stages of prostate cancer, degarelix was shown to be non-inferior to a luteinising hormone releasing hormone (LHRH) agonist in suppressing testosterone levels over a one year treatment period without an initial testosterone flare.

This SMC advice takes account of the benefits of a patient access scheme (PAS) that improves the cost-effectiveness of degarelix. This SMC advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Degarelix is a gonadotropin-releasing hormone (GnRH) antagonist indicated for the treatment of adult male patients with advanced hormone-dependent prostate cancer.

Dosing Information

Starting dose: 240mg (administered as two 120mg/3mL subcutaneous injections).
Maintenance dose: 80mg/4mL administered as one subcutaneous injection every month.

Product availability date

5 May 2009

Summary of evidence on comparative efficacy

Degarelix is a novel testosterone ablating therapy that acts as an antagonist at the gonadatropin releasing hormone (GnRH) receptor. It induces a rapid and sustainable decrease in both testosterone and prostate specific antigen (PSA) levels, without an initial testosterone surge after administration, thereby negating the need for short-term treatment with an anti-androgen (AA).

One phase III open label study was conducted in 610 men aged 18 years or over with histologically confirmed prostate cancer (all stages) for which hormone therapy was indicated. Patients were required to have testosterone levels >1.5 nanogram/mL, an Eastern Cooperative Oncology Group score ≤2, and a PSA level ≥2 nanogram/mL. Patients were randomised equally (stratified according to geographical region and body weight) to degarelix 240mg (two 120mg/3mL injections) on day one followed by 80mg/4mL monthly (240/80), degarelix 240mg on day one followed by 160mg/4mL monthly (240/160), or leuprorelin acetate 7.5mg (as an approximately 1mL intramuscular injection) monthly. The degarelix 240mg/160mg and leuprorelin acetate 7.5mg dose regimens are not licensed in the UK. Degarelix was administered as a subcutaneous injection. Clinical flare protection (generally with bicalutamide 50mg once daily orally) was given to patients in the leuprorelin group at the discretion of the investigator.

The primary endpoint was the probability of achieving castrate levels of testosterone (≤0.5 nanogram/mL) between days 28 and 364, and was considered a treatment response. The treatment response was assessed by whether the lower limit of the 95% confidence interval (CI) for the cumulative probability of testosterone ≤0.5 nanogram/mL (at any monthly measurement from day 28 to day 364) was ≥90%. In addition, non-inferiority of degarelix versus leuprorelin acetate was assessed using a non-inferiority margin of -10%. Secondary endpoints included percent change in PSA from baseline to day 14 and day 28, time to PSA failure and testosterone surge. The primary efficacy outcome was assessed in the intention to treat (ITT) population and comprised patients who had received at least one dose of study medication.

All treatment regimens were able to maintain testosterone suppression from 28 to 364 days. In addition the non-inferiority of degarelix versus leuprorelin acetate in achieving and maintaining testosterone ≤0.5 nanogram/mL was demonstrated (see table below).

Table: testosterone response rate; cumulative probability of a testosterone level ≤0.5 nanogram/mL from days 28 to 364 (Kaplan-Meier estimate of individual response rates)

	Degarelix 240/80mg (ITT, n=207)	Degarelix 240/160mg (ITT, n=202)	Leuprorelin acetate 7.5mg (ITT, n=201)
Responders n (%; 95% CI)	202 (97.2; 93.5 to 98.8)	199 (98.3; 94.8 to 99.4)	194 (96.4; 92.5 to 98.2)
Difference compared to leuprorelin in % responders (97.5% CI)	0.9 (-3.2 to 5.0)	1.9 (-1.8 to 5.7)	-

Table: Testosterone response rate – cumulative probability of a testosterone level ≤0.5nanograms/mL from days 28 to 364 (Kaplan-Meier estimate of individual response rates). ITT = intention-to-treat population, CI = confidence interval

At day 14, PSA levels had declined from baseline by 64%, 65% and 18% in the degarelix 240/80, degarelix 240/160 and leuprorelin acetate groups respectively and at day 28 the reductions were 85%, 83% and 68% respectively. The differences between the degarelix and leuprorelin treatment groups were statistically significant at days 14 and 28. However in the subgroup of patients receiving leuprorelin acetate and bicalutamide, the PSA reduction was similar to that in the degarelix groups. The probability of PSA failure (defined as PSA increase ≥50% from nadir and ≥5 nanogram/mL on two consecutive occasions at least two weeks apart) was similar among the three groups; 8.9% (95% confidence interval [CI] 5.5 to 14.1%) for degarelix 240/80; 14.2% (9.9 to 20.2%) for the degarelix 240/160 group; and 14.1% (9.8 to 20.1%) for the leuprorelin acetate group. A post hoc analysis of PSA failure rates combined the probability of PSA failure with the probability of death. The difference in risk of this combined endpoint between degarelix 240/80 and leuprorelin acetate was of borderline significance (p=0.05).

A testosterone surge was observed in 80% (161/201) patients on leuprorelin acetate; 81% (144/178) of patients without bicalutamide and 74% (17/23) on bicalutamide. No patients on degarelix 240/80mg and one patient on degarelix 240/160mg experienced a testosterone surge.

Results from the European Organisation for Research and Treatment of Cancer QLQ-C30 and the Short Form-12 v2 (SF-12 v2) quality of life questionnaires showed no discernible differences in quality of life across the three treatment groups.

Patients who completed this one-year study entered a 5-year extension phase in which degarelix patients continued previous treatment and leuprorelin acetate patients were re-randomised to one of the two degarelix groups. The extension is ongoing but interim results indicate a significant reduction in the rate of PSA failure or death in patients switched from leuprorelin acetate to degarelix, while there was no significant difference for patients continuing on degarelix.

Summary of evidence on comparative safety

The proportions of patients with treatment-emergent adverse events (AE) were comparable across the treatment groups. The most frequently reported AE for both degarelix and leuprorelin acetate patients during the study were flushing events; 53/207 (26%) in the degarelix 240/80 group, 52/202 (26%) in the degarelix 240/160 group and 43/201 (21%) in the leuprorelin acetate group. A significantly greater proportion of patients in the leuprorelin acetate group reported arthralgia versus those in the degarelix groups (9% versus 4%). The incidence of urinary tract infections was also significantly higher in the leuprorelin acetate than in the degarelix treated patients (9% versus 3%). However, chills (which generally occurred 5 to 10 hours after administration of degarelix and typically lasted less than 24 hours) were experienced by 18/409 (4%) of patients receiving degarelix versus no patients in the leuprorelin acetate group.

The rate of injection site reactions were 35% (73/207), 44% (89/202) and <1% (1/201) for the degarelix 240/80, degarelix 240/160 and leuprorelin acetate groups respectively and were mainly mild or moderate in intensity. In the degarelix group injection site reactions occurred mostly within the month after the first dose and decreased over time. Five (1%) patients were withdrawn from treatment as a result of local injection site reactions.

The Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA) raised concerns over the long-term efficacy and safety for patients developing antibodies against degarelix. Consequently it is noted in the summary of product characteristics (SPC) that anti-degarelix antibody development has been observed in 10% of patients after treatment with degarelix for one year. The SPC goes on to note that there is no indication that the efficacy or safety is affected by antibody formation after one year of treatment.

Summary of clinical effectiveness issues

There are a number of limitations with respect to the pivotal study. Firstly, the dose of leuprorelin acetate used in the study is double the dose licensed in the UK although differences in clinical effectiveness between leuprorelin 3.75mg and 7.5mg have not been established. Secondly, AA cover (to prevent testosterone flare) for patients on leuprorelin acetate was given at the discretion of the investigator and in only 11% of patients. Testosterone flare may cause exacerbation of tumour growth and associated symptoms. The National Institute for Health and Clinical Excellence (NICE) recommend that on commencement of Luteinising Hormone Releasing Hormone (LHRH) agonist therapy, a short course of anti-androgen therapy should be implemented. Thirdly, the study period was one year and therefore the efficacy and safety of degarelix beyond one year is not known. Results of a 5-year extension of this study are awaited. Futhermore, the study population included patients with localised- (31%) and those with non-classifiable disease (19%). The UK marketing authorisation restricts use to patients with advanced disease, 50% of the study population.

A post hoc analysis of the probability of PSA failure and death identified a difference in risk between degarelix 240/80mg and leuprorelin of borderline significance, with a hazard ratio of 0.664 (95% CI 0.385 to 1.146) for patients given degarelix. A sub-group analysis of patients with a baseline PSA level >20nanograms/mL identified a statistically significant lower risk of

PSA failure with degarelix, although other baseline characteristics may not have been matched in these sub-groups. No patients with baseline PSA level <20nanograms/mL experienced PSA failure.

The EMA acknowledges that the major clinical added value of degarelix was the avoidance of the testosterone flare seen with LHRH agonists (in other words, no requirement for concomitant anti-androgen therapy), and they note that degarelix is thus especially useful when a rapid reduction in the testosterone levels is of critical importance. The European Association of Urology (EAU) current guidelines on Prostate Cancer include a comment that the clinical advantage of suppression of the initial flare up is only clinically relevant in a minority of metastatic patients (for example, in patients with impending spinal cord compression). The advantage of degarelix compared to a LHRH agonist plus routine short-term anti-androgen therapy for testosterone flare in the majority of patients is unclear.

Degarelix is administered monthly by subcutaneous injection and the summary of product characteristics states that reconstitution of the powder to the solution for injection may take up to 15 minutes. In comparison the LHRH agonists may be administered every 3 to 12 months and some are available in ready-to-inject formulations. As degarelix administration does not require initial concomitant anti-androgen therapy it may simplify the treatment regimen. The inconvenience of more frequent injection, however, may have disadvantages from the perspective of patients and service delivery.

SMC clinical experts advised that degarelix may have a particular role in the treatment of patients at high risk of spinal cord compression, albeit an unusual scenario in practice.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis comparing degarelix with goserelin plus short-term AA for flare protection in patients with advanced hormone-dependent prostate cancer. A subgroup analysis was also provided which focused on patients at higher risk of disease progression with a baseline PSA level >20nanograms/mL. A lifetime Markov model was used which modelled patients as they progressed from first-line treatment with either degarelix or goserelin to subsequent treatments including AA addition, AA withdrawal and chemotherapy.

Given that subgroup analysis of the key study showed that PSA failure was only experienced in patients with PSA level >20nanograms/mL, the higher risk group may be the more relevant population.

The economic model used data from the secondary endpoint of PSA recurrence from the clinical study and extension phase. Degarelix data were extrapolated over the 20-year time horizon by fitting a Weibull curve. One-year hazard ratios of 1.66 and 1.87 were then applied to model PSA failure in the goserelin group in the ITT and high risk populations respectively. In the ITT population, the PSA failure rate was 63% higher in the goserelin group at the start of year 1 and remained 40% higher at the start of year 10.

Resource use was based on a combination of clinical expert opinion and literature sources and included GP visits, urology outpatient visits and bone scans. The increased drug and

administration costs associated with degarelix were offset largely due to the difference in PSA failure rate resulting in patients in the goserelin arm progressing to the more expensive subsequent treatments earlier in the model.

Utility values used in the model were 0.9 for patients responding to either first or second-line therapies and 0.4 for patients who are being treated with chemotherapy or palliative care as their prostate cancer has become hormone-resistant. These values were selected from the literature based on a review of prostate cancer related quality of life values from both patients and physicians.

In the base case the manufacturer estimated that degarelix would dominate goserelin with estimated savings of £271 and a QALY gain of 0.46. The results of the higher risk subgroup analysis also showed degarelix to be the dominant treatment with cost savings of £1,403 and a QALY gain of 0.49.

A patient access scheme (PAS) was submitted by the manufacturer and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. The PAS involved a simple discount on the price of the drug. When the PAS was included degarelix was estimated to dominate goserelin with increased savings of £2,641 and a QALY gain of 0.46. The results of the higher risk subgroup analysis also showed degarelix to be the dominant treatment with cost savings of £3,204 and a QALY gain of 0.49.

The following weaknesses were noted:

- No data were presented comparing degarelix with goserelin as it was assumed that data from the clinical study relating to leuprorelin could be used for the goserelin arm of the economic model. There were some weaknesses with the clinical data which may impact on the generalisability of the trial results to Scottish practice e.g. the model used the secondary endpoint of PSA recurrence where the difference between the treatment arms in the ITT population was only borderline significant with wide confidence intervals and the post-hoc subgroup analysis was based on low patient numbers.
- Given potential uncertainty regarding the clinical outcomes, a more pessimistic analysis was provided by the manufacturer, assuming only 1 year of benefit with degarelix. This resulted in cost-effectiveness ratios of £9,698 with the PAS in all patients and £4,697 with the PAS in the high risk subgroup only.

Despite these weaknesses the economic case was considered demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission: PROSTaid.

Additional information: guidelines and protocols

In February 2008, NICE published a guideline entitled ‘Prostate cancer: diagnosis and treatment.’

In July 2010, the National Comprehensive Cancer Network (NCCN) published version 3.2010 of an NCCN Clinical Practice Guideline in Oncology for prostate cancer.

NICE and NCCN do not give specific recommendations about degarelix. The NICE guideline predates the licensing of degarelix.

EAU published an updated guideline entitled 'Guidelines on prostate cancer' in April 2010. The guidelines include a comment regarding LHRH antagonists and specifically degarelix, and note that so far its use is limited by a monthly formulation, compared with three-month and six-month depot formulations, (the latter are not available in the UK). The guidelines go on to note that the clinical advantage of the suppression of the initial flare up is only clinically relevant in a minority of metastatic patients, and finally [LHRH] antagonists must confirm their efficacy in the long-term, most available trials being limited to a one-year follow-up period.

Guidance developed by a collaboration of the Uro-oncology Group, the British Association of Urological Surgeons and the British Prostate Group in 2009 - Multi-disciplinary Team guidance for managing prostate cancer consider gonadotropin-releasing hormone antagonists, such as degarelix, to be clinically equivalent to LHRH agonists, without causing the testosterone surge seen with LHRH agonists.

Additional information: comparators

Androgen withdrawal therapy for advanced prostate cancer may take the form of surgical castration (bilateral orchidectomy) or chemical castration with long-acting LHRH agonists which include buserelin, goserelin, histrelin, leuprorelin or triptorelin. Medical castration with anti-androgens that antagonise effects at the androgen receptor (bicalutamide, cyproterone acetate, flutamide) may be appropriate for selected patients (bicalutamide is not indicated in patients with metastatic disease).

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Degarelix injection	**240mg starting dose, followed by 80mg as a subcutaneous injection monthly**	**1,683 in first year, 1,552 thereafter**
LHRH agonists[Δ]		
Buserelin nasal spray (Suprefact)	One 100microgram spray into each nostril six times daily.	1,324
Goserelin 10.8mg implant	One implant every 12 weeks	1018
Triptorelin 3.75mg injection (Gonapeptyl Depot®)*	One 3.75mg dose administered by intramuscular injection every 28 days.	1,062
Histrelin 50mg implant	One implant every 12 months	990
Leuprorelin acetate 3.75mg injection	One injection every month.	903
Leuprorelin acetate 11.25mg injection	One injection every three months.	903
Triptorelin 3mg injection	One injection every 28 days.	897

(Decapeptyl® SR)		
Goserelin 3.6mg implant	One implant every 28 days	845
Triptorelin 11.25mg injection (Decapeptyl® SR)	One injection every three months.	828
Goserelin 3.6mg implant	One implant every 28 days	760
Anti-androgens		
Cyproterone acetate 100mg tablets	200 to 300mg daily in divided doses	635 to 952
Flutamide 250mg tablets	250mg three times daily	289
Bicalutamide 150mg tablets**	150mg once daily	218

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 04/10/2010, except costs for degarelix, which are from MIMS, September 2010.
$^{\Delta}$ Cost for short-term anti-androgen use (3-week course) during initial dosing of LHRH would be: cyproterone acetate 300mg daily in divided doses, £55, flutamide 250mg three times daily, £17, or bicalutamide 50mg once daily, £6 (unlicensed use).
*Gonapeptyl Depot® has not been recommended by SMC for use in NHS Scotland.
** bicalutamide is not licensed for metastatic prostate cancer

Additional information: budget impact

Based on an estimated market share of 2.5% in year 1 and 11% in year 5 the manufacturer estimated that 35 patients would be treated with degarelix in year 1 rising to 811 patients in year 5. The corresponding net drug budget impact was estimated at £24k in year 1 and £526k in year 5. When the PAS was included the net budget impact was estimated to be £6k in year 1 rising to £118k in year 5. These figures relate to the licensed population and assume LHRH agonists are displaced. The budget impact in a high risk subgroup would be lower.

References

The under-noted references were supplied with the submission.

Klotz L, Boccon-Gibod L, Shore ND et al. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. BJU Int 2008; 102**:** 1531–38

Crawford ED, Moul JW, Shore ND et al. Abstract 670: Switching from leuprolide to degarelix vs continuous degarelix treatment – effects on long-term prostate-specific antigen control. J Urol 2010; 183(Suppl): e262

Tombal B, Miller K, Boccon-Gibod L et al. Additional analysis of the secondary end point of biochemical recurrence rate in a phase 3 trial (CS21) comparing degarelix 80mg versus leuprolide in prostate cancer patients segmented by baseline characteristics. European Urology 2010; 57: p836-42

This assessment is based on data submitted by the applicant company up to and including 02 December 2010.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

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

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.