

Degarelix: a new hormonal treatment for prostate cancer

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According to NICE, prostate cancer constitutes about 25% of new diagnoses of malignant cancer in men in England and Wales.¹ The largest single area of spending on cancer drugs is on hormonal therapy, accounting for about 40% of the £292 million total. This article focuses on a novel hormonal treatment for prostate cancer, degarelix.

Prostate cancer is now the most frequently diagnosed cancer in European and American men.^{2,3} In the UK, prostate cancer accounts for around one-quarter of all new male cancer diagnoses^{1,4} and the incidence appears to be increasing.⁴ Prostate cancer incidence rates increase steeply with age.¹ In Europe, prostate cancer mortality has increased by about 16% since 1995,¹ largely as a result of the rapid rise in the ageing male population.

Prostatic epithelial cells depend on androgens for proliferation, differentiation and function, and the androgen, testosterone, is essential for prostatic tumour cell proliferation and survival. Most of the androgens originate from the testes (only around 5–10% are derived from adrenal biosynthesis). Testicular testosterone secretion is regulated by the hypothalamic-pituitary-gonadal axis (Figure 1). The hypothalamic gonadotrophin-releasing hormone (GnRH) stimulates the anterior pituitary gland to release luteinising hormone (LH) and follicle-stimulating

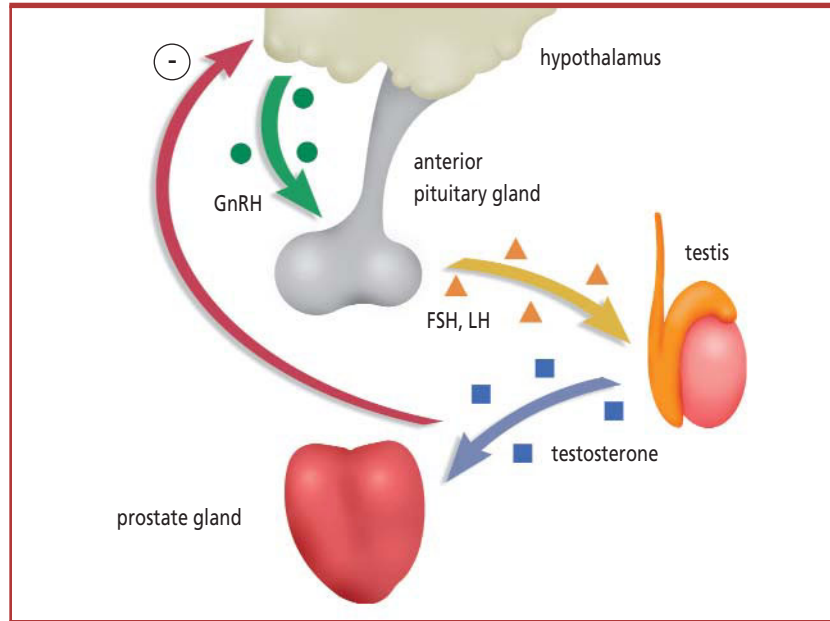


Figure 1. Regulation of testosterone secretion by the hypothalamic-pituitary-gonadal axis. GnRH, gonadotrophin-releasing hormone; FSH, follicle-stimulating hormone; LH, luteinising hormone.

hormone (FSH), which stimulate testosterone release from the testes. Testosterone, in turn, stimulates prostate cancer cell proliferation via the action of its active metabolite, dihydrotestosterone, on androgen receptors in the prostate cells; circulating testosterone exerts a negative feedback control on hypothalamic LH secretion.

If prostate cells are deprived of androgenic stimulation, they undergo apoptosis. Thus suppression of androgen action forms the basis of androgen deprivation therapy (ADT).⁵ In advanced disease, the mainstay of treatment is ADT, which can provide effective palliation.⁶

CURRENT OPTIONS FOR TESTOSTERONE REDUCTION IN PROSTATE CANCER

Since the advent of ADT in 1941,⁷ the gold-standard therapy has been

surgical castration (orchidectomy). However, because of the irreversibility and negative psychological effect of orchidectomy, medical castration with GnRH agonists has become the standard of care in the hormonal therapy of advanced prostate cancer.⁵

Current therapy

GnRH agonists act by stimulating the natural GnRH receptors in cells of the anterior pituitary gland. Constant exposure to such high-affinity stimulation in the therapeutic context results in downregulation of pituitary receptors, inhibition of FSH and LH release, and a concurrent reduction in testosterone production.⁸ Randomised trials suggest that, as a class, GnRH agonists are similar to orchidectomy for the treatment of metastatic prostate cancer, in terms of patient

survival.⁹ For example, in a multi-centre, randomised trial in the UK and Ireland in patients with previously untreated metastatic prostate cancer, there was no difference in overall survival between the GnRH analogue, goserelin, and orchidectomy at a median follow-up of two years.¹⁰ However, while GnRH agonists have the desired clinical effect in terms of castration, they stimulate testosterone production before shutting it down. The initial testosterone surge can result in a transient increase (flare) in prostate cancer growth and in some patients can lead to a worsening of symptoms attributable to rapid cancer growth, such as bone pain and urinary obstruction, known as the flare phenomenon.^{8,11} For this reason, patients beginning GnRH agonist therapy are generally also treated with short-term (*eg* three weeks' duration) oral anti-androgen therapy to prevent flare. However, it is less well known that patients may also experience additional surges in testosterone level during long-term treatment upon re-administration of GnRH agonists (acute-on-chronic flare response or microsurge); testosterone surges may also occur at any time during treatment (breakthrough response).¹²

Breakthrough increases of serum testosterone in medically castrated patients with prostate cancer could have clinical implications regarding prostate-specific antigen (PSA) progression. In one study, patients with breakthrough increases in testosterone of $>32\text{ ng/dL}$ had a significantly shorter survival free of androgen-independent progression than patients without these events (Figure 2).¹³ Conversely, there is evidence suggesting that intermittent ADT may offer equivalent efficacy to continuous ADT,¹⁴ and this may be a complex issue.

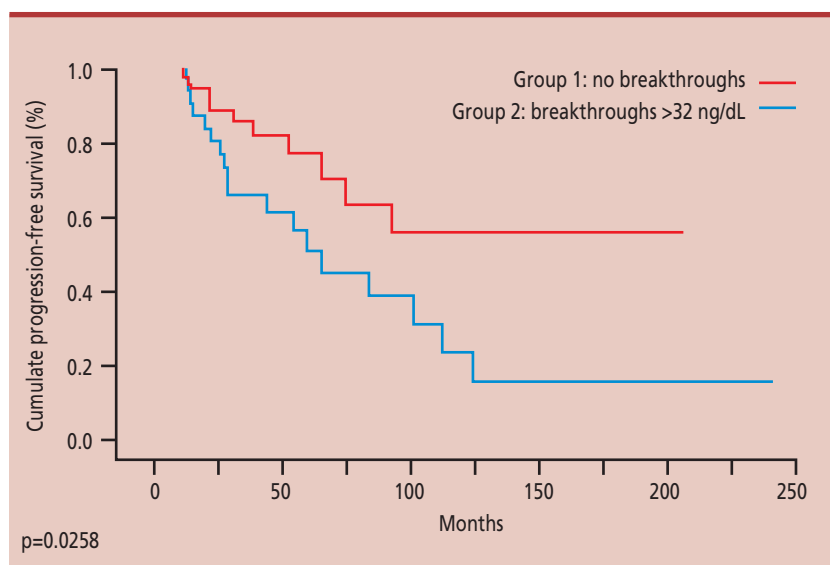


Figure 2. Survival free of androgen-independent progression analysis according to serum testosterone behaviour in relation to lowest castrate threshold established at 32 ng/dL . Group 1, patients with all three serum testosterone determinations $<32\text{ ng/dL}$. Group 2, patients with breakthrough increases $>32\text{ ng/dL}$.

Moreover, several conventional GnRH agonists do not achieve castrate levels of testosterone (defined as $\leq 50\text{ ng/dL}$) in 1–12.5% of patients or fail to achieve levels comparable to orchidectomy (20 ng/dL) in 13–40% of patients.^{15–18} Furthermore, serum levels of testosterone are rapidly reduced by orchidectomy with castrate levels of testosterone occurring after about 2.5 hours.¹⁹ In contrast, with GnRH agonists, castration is delayed, with lower testosterone levels only achieved 2–4 weeks after the initial injection.²⁰

GnRH BLOCKERS

GnRH blockers are a new class of hormonal agents that occupy GnRH receptor sites without activation, producing an immediate and pronounced suppression of testosterone without an initial surge.²¹ However, some GnRH antagonists have been associated with serious histamine-mediated side-effects⁵ due to excess histamine release from mast cells. Abarelix, the first antagonist to undergo clinical development, was associated with an increased risk of

immediate-onset systemic allergic reactions²² and was withdrawn voluntarily in the USA in 2005.

DEGARELIX

Degarelix is a new GnRH blocker, due to be launched in the UK in 2009. This article reviews the properties of degarelix and the evidence supporting its use in patients with prostate cancer.

Pharmacology/mode of action

GnRH blockers, such as degarelix, inhibit the production of testosterone in men by directly and competitively blocking pituitary GnRH receptors. This blockade directly suppresses the secretion of LH and FSH and thereby reduces the production of testosterone by the testes.

Degarelix is the product of a targeted peptide development programme; its biochemical structure comprises a synthetic linear decapeptide amide modelled on normal human GnRH. During development, structural modifications were introduced with the aim of reducing the agent's histamine-releasing potential, while maintaining or increasing drug

potency. Moreover, degarelix is water-soluble and, upon subcutaneous (sc) administration, forms a unique gel-like depot without any additional vehicle being present. This results in a sustained release of the compound into the circulation,²³ ensuring that a long-lasting clinical effect is maintained.

In animal studies, degarelix produced rapid, long-lasting and dose-dependent suppression of the pituitary gonadal axis as revealed by the decrease in plasma LH and testosterone levels.²⁴ In a rat model of prostate cancer, degarelix suppressed testosterone to castrate levels within two days and maintained such levels throughout the study. In this model, degarelix also showed similar control of tumour volume compared to surgical castration.²³ In a study on rat peritoneal mast cells, degarelix displayed only weak histamine-releasing properties, and of the antagonists tested (Nal-Glu, cetrorelix, ganirelix, azaline B and abarelix), it possessed the lowest propensity to release histamine.²⁴

In healthy volunteers, degarelix rapidly reduces levels of LH, and there is a rapid reduction of testosterone to castrate levels.²⁵ The half-life of degarelix is substantially longer after sc and intramuscular (im) administration than after intravenous (iv) injection, due to depot formation in body tissues (gel depot formation with iv administration was avoided by the use of microgram doses).

Efficacy

Two open-label, randomised, dose-finding phase II trials conducted in Europe²⁶ and North America²⁷ established the doses of degarelix to be used in phase III of clinical development. In the North American study, 127 patients received an initial dose of 200mg followed by monthly maintenance doses of 60 or 80mg. In the European study, 187 patients

received an initial dose of either 200 or 240mg followed by monthly maintenance doses of 80, 120 or 160mg. Both studies showed that degarelix induced fast, profound and sustained testosterone and PSA suppression in prostate cancer patients, without evidence of testosterone surge or clinical flare. From these studies, 240mg was established as the most effective induction dose of degarelix and 80 and 160mg as the most suitable maintenance doses. These doses were further investigated in the phase III setting.

Phase III study

A pivotal, randomised controlled phase III trial showed that degarelix (starting dose of 240mg and monthly maintenance doses of 80 or 160mg) was as effective as the GnRH agonist leuprolide (standard monthly 7.5mg dose) in maintaining low testosterone levels (0.5ng/mL) over a one-year treatment period.²⁸ The trial involved 610 prostate cancer patients (any stage; median age 72 years) requiring ADT. Degarelix was administered by sc injection and leuprolide by im injection.

Both degarelix doses were as effective as leuprolide at inducing and

sustaining testosterone suppression to castrate levels (0.5ng/mL) throughout the one-year study (Figure 3). The degarelix regimens of 240/80 and 240/160mg achieved a more rapid reduction of testosterone than leuprolide (Figure 4). Thus, with degarelix, median testosterone level was reduced by >90% by day three, compared with a 65% increase in the median testosterone level in the leuprolide group. Indeed, median testosterone levels in the leuprolide group were above castrate levels (>0.5ng/mL) until the measurements on day 28.

In the leuprolide group, the anti-androgen, bicalutamide, could be administered at the start of treatment for clinical flare protection at the discretion of the investigator. A surge in testosterone (defined as a testosterone increase of $\geq 15\%$ from baseline, on any two days during the first two weeks) occurred in 81% of patients receiving leuprolide alone and in 74% of those receiving leuprolide plus antiandrogen (11% of all leuprolide patients received concomitant bicalutamide). Testosterone increases of >0.25ng/mL (microsurges) occurred in eight patients (4%) in the leuprolide group, with

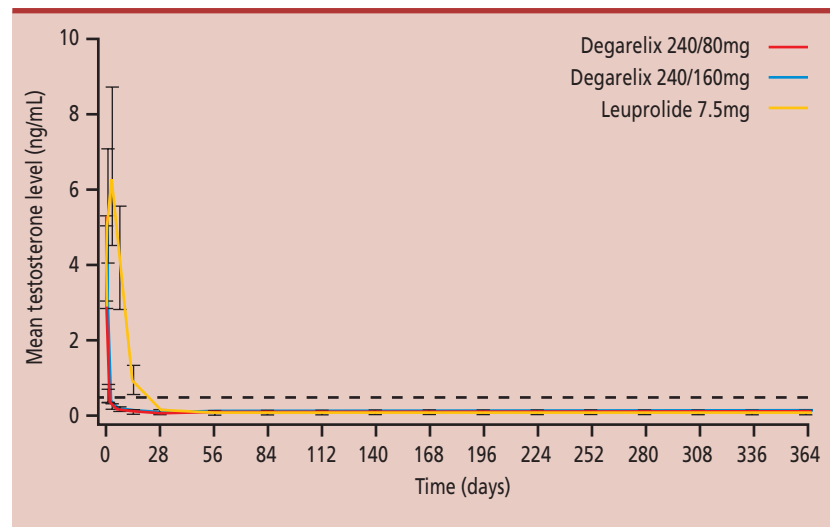


Figure 3. Median (quartile) serum testosterone levels over time with degarelix or leuprolide (dotted line represents typical castrate level of testosterone)²⁸

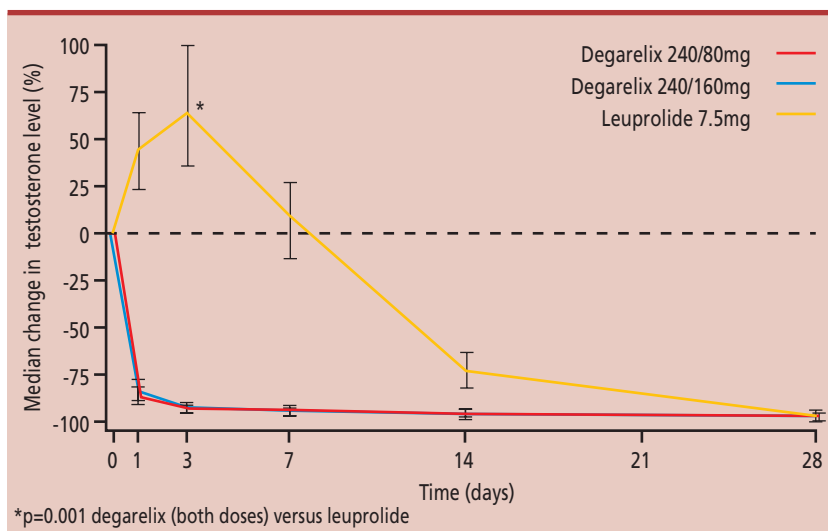


Figure 4. Median serum testosterone during the first month of treatment with degarelix or leuprolide²⁸

testosterone breakthrough ($>0.5\text{ng/mL}$) occurring in four of these patients (2%). Neither dosing schedule of degarelix induced testosterone surge or microsurge, both of which were seen with leuprolide.

The steady decrease in PSA levels in all treatment groups during the one-year study provided biochemical evidence of clinical response. However, degarelix was associated with a more rapid reduction in PSA levels than leuprolide (Figure 5). Degarelix reduced PSA levels at day 14 (by 64% with degarelix 240/80mg, 65% with degarelix 240/160mg) and day 28 (85% and 83%, respectively) to a significantly greater extent than leuprolide (reductions of 18% and 68% after 14 and 28 days, respectively; both $p<0.001$). PSA suppression was maintained throughout the study. Degarelix monotherapy also provided a similar PSA decrease to that achieved with leuprolide plus antiandrogen for flare protection. The incidence of PSA failure (PSA increase $\geq 50\%$ from nadir and $\geq 5\text{ng/mL}$ on two consecutive occasions at least two weeks apart) was 14.1% with leuprolide versus 8.9% with degarelix 240/80mg and 14.2% with degarelix 240/160mg.

Tolerability

In a worldwide clinical development programme that started in 1996, degarelix has been administered to over 2000 patients²⁹ including patients with prostate cancer in two phase II and one phase III trials^{26–28} with no reported cases of immediate-onset systemic allergic reactions, to date. The most frequently reported side-effect associated with degarelix therapy is hot flushes, an expected androgen withdrawal symptom. Other common adverse events reported in these clinical trials of degarelix included fatigue, back pain, arthralgia and urinary tract infection.

In the pivotal phase III trial, there was a higher incidence of injection-site reactions with degarelix compared with leuprolide (40% versus $<1\%$; $p<0.001$, respectively); resulting in discontinuation in about 1% of the patients receiving degarelix. These reactions occurred predominantly after the first injection (33% of starting-dose injections versus 4% of maintenance-dose injections) and were mostly of mild-to-moderate intensity. The difference in incidence of injection-site reactions might be due to the different routes of

administration (sc versus im) and the injection volume. Local injection-site reactions have previously been reported with GnRH agonists when given sc.^{30,31}

POTENTIAL USE IN PRACTICE/PLACE IN THERAPY

Degarelix represents a new effective therapy for inducing and maintaining androgen deprivation in patients with prostate cancer. It binds directly to and blocks GnRH receptors offering a simpler more direct mechanism of action compared with GnRH agonists and one that may better mimic orchidectomy. The implications of testosterone microsurges and testosterone breakthrough, both characteristic of GnRH agonist therapy but absent with degarelix, merit further investigation, especially as the significance of extremely low levels of androgen in patients with prostate cancer is becoming better understood.

When administered in the clinic, degarelix forms a unique sustained-release depot that allows a steady and controlled release of the drug into the circulation and ensures a long-lasting clinical effect. Degarelix produces a rapid, profound and sustained reduction in serum testosterone and PSA without the initial stimulation seen with GnRH agonists and with no evidence of systemic allergic reactions. Its immediate onset of action achieves a faster control of testosterone and PSA levels than GnRH agonists such as leuprolide. Moreover, the absence of testosterone surge with degarelix allows degarelix monotherapy to achieve PSA suppression without the need for concomitant antiandrogen for flare protection. The absence of testosterone microsurges after repeated administration of degarelix may translate to longer-term benefits through effective testosterone control.¹³

Marketing authorisation for a degarelix 240mg starting dose and an

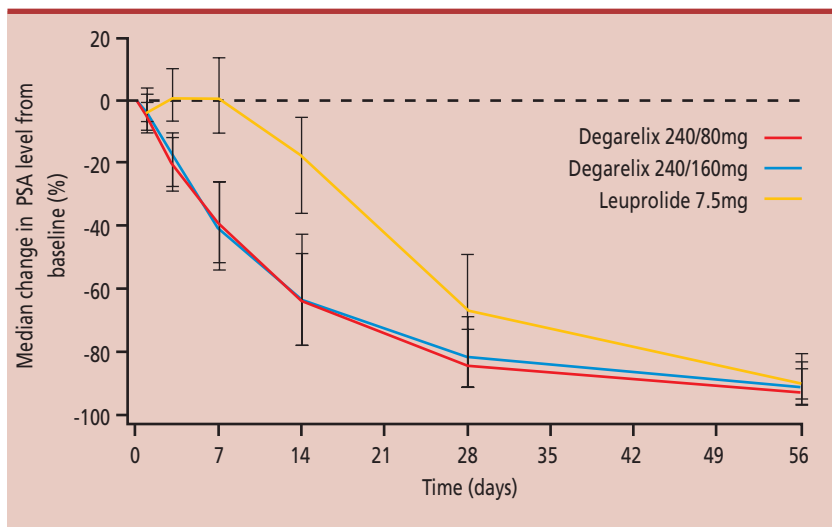


Figure 5. Median percentage change in PSA levels in patients treated with degarelix and leuprolide during the first two months of treatment²⁸

80mg monthly maintenance dose is expected in early 2009 from both European and US regulatory agencies. Further direct comparisons of degarelix and GnRH agonists in randomised controlled trials will establish the optimal approach to the long-term management of prostate cancer and the role of degarelix in treatment.

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REFERENCES

1. Cancer Research UK. UK prostate cancer incidence statistics (<http://info.cancerresearchuk.org/cancerstats/types/prostate/incidence/>; accessed 1 December 2008).
2. Ferlay J, Autier P, Boniol M, et al. Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol* 2007;18:581–92.
3. American Cancer Society. Overview: prostate cancer – how many men get prostate cancer? (http://www.cancer.org/docroot/CRI/content/CRI_2_2_1X_How_many_men_get_prostate_cancer_36.asp?sitearea; accessed 28 November 2008).
4. National Institute for Health and Clinical Excellence. *Prostate cancer: diagnosis and treatment*. National Collaborating Centre for Cancer 2008 (<http://www.nice.org.uk/nicemedia/pdf/CG58FullGuideline.pdf>; accessed 1 December 2008).
5. Heidenreich G, Aus CC, Abbou M, et al. Guidelines on prostate cancer 2007. European

Association of Urology. (http://www.uroweb.org/fileadmin/tx_eauguidelines/Prostate%20Cancer.pdf; accessed 28 November 2008).

6. Michaelson MD, Cotter SE, Gargollo PC, et al. Management of complications of prostate cancer treatment. *CA Cancer J Clin* 2008;58:196–213.
7. Huggins C, Hodges CU. Studies on prostate cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Res* 1941;1:29–37.
8. Hellerstedt BA, Pienta KJ. The current state of hormonal therapy for prostate cancer. *CA Cancer J Clin* 2002;52:154–79.
9. Seidenfeld J, Samson DJ, Hasselblad V, et al. Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. *Ann Intern Med* 2000;132:566–77.
10. Kaisary AV, Tyrrell CJ, Peeling WB, et al. Comparison of LHRH analogue (Zoladex) with orchiectomy in patients with metastatic prostatic carcinoma. *Br J Urol* 1991;67:502–8.
11. Thompson IM. Flare associated with LHRH-agonist therapy. *Rev Urol* 2001;3 Suppl 3:S10–4.
12. Tombal B, Berges R. How good do current LHRH agonists control testosterone? Can this be improved with Eligard? *Eur Urol Suppl* 2005;4:30–6.
13. Morote J, Orsola A, Planas J, et al. Redefining clinically significant castration levels in patients with prostate cancer receiving continuous androgen deprivation therapy. *J Urol* 2007;178:1290–5.
14. Miller K, Steiner U, Lingnau A, et al. Randomised prospective study of intermittent versus continuous androgen suppression in advanced prostate cancer. *J Clin Oncol* 2007; ASCO Meeting Abstracts; 25(18S):5015.
15. Tombal B. The importance of testosterone control in prostate cancer. *Eur Urol Suppl* 2007;6:834–9.
16. Oefelein MG, Cornum R. Failure to achieve castrate levels of testosterone during luteinizing

hormone releasing hormone agonist therapy: the case for monitoring serum testosterone and a treatment decision algorithm. *J Urol* 2000;164:726–9.

17. Morote J, Esquena S, Abascal JM, et al. Failure to maintain a suppressed level of serum testosterone during long-acting depot luteinizing hormone-releasing hormone agonist therapy in patients with advanced prostate cancer. *Urol Int* 2006;77:135–8.
18. Sarosdy MF, Schellhammer PF, Soloway MS, et al. Endocrine effects, efficacy and tolerability of a 10.8-mg depot formulation of goserelin acetate administered every 13 weeks to patients with advanced prostate cancer. *BJU Int* 1999;83:801–6.
19. Arcadi JA. Rapid drop in serum testosterone after bilateral subcapsular orchiectomy. *J Surg Oncol* 1992;49:35–8.
20. Tombal B. What is new in hormone therapy for prostate cancer in 2007? *Eur Urol Suppl* 2008; 7:477–83.
21. Van Poppel H, Nilsson S. Testosterone surge: rationale for gonadotropin-releasing hormone blockers? *Urology* 2008;71:1001–6.
22. Hogle WP. Abarelix (Plenaxis™). *Clin J Oncol Nurs* 2004;8:663–5.
23. Princivalle M, Broqua P, White R, et al. Rapid suppression of plasma testosterone levels and tumor growth in the Dunning rat model treated with degarelix, a new gonadotropin-releasing hormone antagonist. *J Pharmacol Exp Ther* 2007; 320:1113–8.
24. Broqua P, Riviere PJ, Conn PM, et al. Pharmacological profile of a new, potent, and long-acting gonadotropin-releasing hormone antagonist: degarelix. *J Pharmacol Exp Ther* 2002;301:95–102.
25. Balchen T, Agersø H, Oleson TK, et al. Pharmacokinetics, pharmacodynamics and safety of a novel fast-acting gonadotropin-releasing hormone receptor blocker, degarelix, in healthy men. 8th International Symposium on GnRH Analogues in Cancer and Human Reproduction, Salzburg, Austria, 10–13 February 2005.
26. Van Poppel H, Tombal B, de la Rosette JJ, et al. Degarelix: a novel gonadotropin-releasing hormone (GnRH) receptor blocker – results from a 1-yr, multicentre, randomised, phase 2 dosage-finding study in the treatment of prostate cancer. *Eur Urol* 2008;54:805–13.
27. Gittelman M, Pommerville PJ, Persson B-E, et al. A 1-year, open-label, randomized phase II dose-finding study of degarelix, a novel gonadotropin-releasing hormone (GnRH) receptor blocker, in the treatment of prostate cancer in North America. *J Urol* 2008;180:1986–92.
28. 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 prostate cancer patients. *BJU Int* 2008;102:1531–8.
29. Ferring, data on file.
30. Oka D, Shiba M, Arai Y et al. Skin reactions to 3-month depot type of luteinizing hormone-releasing hormone agonist therapy. *JMAJ* 2006; 49:48–54.
31. Sanofi-aventis. Eligard (7.5mg), US product label. November 2007.