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Degarelix

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Contents

Abstract

▲ Degarelix is a gonadotropin-releasing hormone (GnRH) receptor antagonist that, in common with GnRH receptor agonists (e.g. leuprolide, goserelin and triptorelin), is indicated for use as an androgen-deprivation therapy in patients with advanced prostate cancer.

▲ In 1-year, randomized, open-label, phase II or III trials in patients with all stages of prostate cancer, subcutaneous degarelix was associated with rapid, profound and sustained suppression of serum testosterone and prostate-specific antigen (PSA), without evidence of testosterone surges or microsurges.

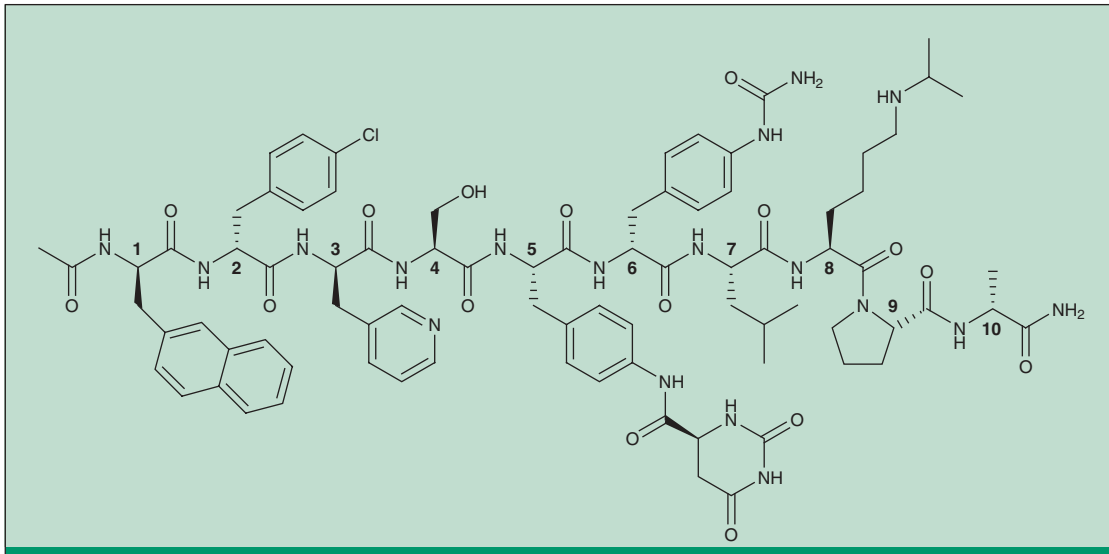
▲ In the phase III trial, degarelix (240 mg initially followed by 80 mg every 28 days) was considered to be effective and noninferior to intramuscular leuprolide (7.5 mg every 28 days) with regard to inducing and maintaining suppression of serum testosterone to castrate levels (i.e. ≤0.5 ng/mL).

▲ Degarelix induced testosterone suppression more rapidly than leuprolide. Median serum testosterone levels of ≤0.5 ng/mL were achieved by day 3 in degarelix recipients, but not until day 28 in leuprolide recipients.

▲ PSA suppression was also more rapid with degarelix than with leuprolide, with significant between-group differences in serum PSA levels favouring degarelix at 14 and 28 days.

▲ Degarelix treatment for 1 year was generally well tolerated; the adverse events reported were mostly related to subcutaneous drug administration (i.e. injection-site reactions) and hormonal androgen deprivation (e.g. hot flushes).

Features and properties of degarelix (Firmagon®)	
Indication	
Advanced prostate cancer	
Mechanism of action	
Gonadotropin-releasing hormone receptor antagonist	
Dosage and administration	
Route of administration	Subcutaneous
Initial dose	240 mg
Maintenance dose	80 mg every 28 d
Pharmacokinetic properties (actual value or, where indicated, population pharmacokinetic model estimate, based on subcutaneous administration of a single dose of degarelix 240 mg [at a concentration of 40 mg/mL] to patients with all stages of prostate cancer)	
Mean peak plasma concentration	66 ng/mL
Mean trough plasma concentration	11–12 ng/mL
Mean area under the plasma concentration-time curve	635 ng • d/mL
Median elimination half-life (model estimate)	43 d
Most common adverse events (in a phase III clinical trial)	
Injection-site reactions, hot flushes (flashes), weight gain and increases in serum levels of hepatic transaminases and γ-glutamyl transferase	



Degarelix

Prostate cancer is the most common malignancy in men; it accounts for between one-fifth and one-quarter of all newly diagnosed cancers in the UK,[1] EU[2] and US.[3] It is also the second or third leading cause of cancer-related death among men in these countries/regions: behind lung cancer in the UK;[1] behind lung cancer, and equal to colorectal cancer, in the US;[3] and behind both lung and colorectal cancer in the EU.[2]

Recommended treatment options for prostate cancer vary according to disease stage at diagnosis, as set out in various US[4,5] and European[1,6] guidelines. Radical prostatectomy and radiotherapy are the standard treatments of curative intent for localized disease (e.g. in intermediate- and high-risk patients for whom watchful waiting or active surveillance is considered inappropriate).[1,6] As androgens appear to play a role in the progression of prostate cancer,[7] androgen-deprivation treatment is the standard palliative therapy for advanced or metastatic disease.[1,5,6,8] Medical castration (i.e. antiandrogen hormonal therapy), which is reversible, but associated with problems with compliance and administration, has largely supplanted irreversible surgical castration (i.e. bilateral orchiectomy) as a means of achieving androgen withdrawal.[1,9,10]

Gonadotropin-releasing hormone (GnRH) receptor agonists (e.g. leuprolide, goserelin and triptorelin) are the current mainstay of hormonal therapy; these agents work by continuously stimulating the pituitary, resulting in desensitization of gonadotropin secretion and thereby suppression of gonadal steroid production.[7,11,12] However, their administration leads to an initial supra-physiological increase (or surge) in luteinizing hormone (LH) activity and serum testosterone levels; this, in turn, produces a transient increase in tumour growth that can exacerbate clinical symptoms ('flare' reaction) and may also adversely affect survival in patients with metastatic disease.[10] Antiandrogen flare protection therapy is routinely given with the first dose of a GnRH agonist, which is associated with the greatest increase in testosterone, although subsequent doses also appear to be accompanied by smaller testosterone surges ('microsurges') with potentially negative prognostic effects.[10]

GnRH receptor antagonists represent a more logical approach to hormonal therapy, since these agents rapidly suppress testosterone levels, without inducing a testosterone surge.[10] Early compounds had histamine-releasing properties and/or solubility or potency limitations that precluded their clinical

usefulness and/or development.[7,13] Newer compounds with reduced histamine-releasing properties that have been approved for the treatment of advanced prostate cancer include abarelix (currently only available in Germany) and degarelix (Firmagon®).[14,15]

This article reviews the pharmacological properties of subcutaneous degarelix, and its efficacy and safety in patients with prostate cancer. Medical literature on the clinical use of degarelix in advanced prostate cancer was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

- GnRH antagonists, such as degarelix, rapidly and reversibly suppress secretion of gonadotropins (LH and follicle-stimulating hormone [FSH]) by competing with endogenous GnRH for binding to specific plasma membrane receptors on anterior pituitary gonadotroph cells (gonadotropes).[7,13,16] The inhibition of LH secretion, in turn, results in suppression of *de novo* synthesis of androgens (including testosterone and dihydrotestosterone [DHT]) in testicular Leydig cells.
- In preclinical studies in rats, subcutaneous degarelix produced a rapid and sustained suppression of the pituitary-gonadal axis[15,17] and demonstrated a longer duration of action than other GnRH antagonists (abarelix, azaline B, cetrorelix and ganirelix).[15] It also inhibited tumour growth to a similar extent as surgical castration in a rat carcinoma model.[17]
- Administration of single-[18] or multiple-dose[19-21] subcutaneous degarelix (using a variety of dosage regimens) was associated with rapid and sustained suppression of gonadotropins and androgens in randomized studies in healthy eugonadal young men (n = 80)[18] and patients with prostate cancer (n = 127–610).[19-21]
- In a double-blind, placebo-controlled, phase I, dose-escalation study in healthy eugonadal young men,[18] single injections of degarelix 0.5–40 mg (at concentrations of 5–30 mg/mL[22]) dose-dependently reduced serum testosterone levels to below the castrate level (0.5 ng/mL) within 24 hours. Testosterone suppression <0.5 ng/mL was maintained for more than 2 months in the men receiving degarelix 40 mg; suppression of serum levels of DHT, LH and FSH were also observed.[18] See section 3 for a discussion of hormone levels observed in trials in patients with prostate cancer.

2. Pharmacokinetic Profile

This section includes pharmacokinetic data for subcutaneous degarelix derived from the US prescribing information,[23] the EU summary of product characteristics (SPC),[24] the European Medicines Agency (EMEA) assessment report,[25] the US FDA clinical pharmacology and biopharmaceutics review[26] and a pivotal phase III study in patients with prostate cancer[21] (see section 3 for a discussion of the design and results of this study). Degarelix is currently manufactured in a liquid phase peptide synthesis process; where available, pharmacokinetic data for this formulation (which was used in the phase III trial[21]) are presented.

- After subcutaneous administration, degarelix forms a depot from which the drug is released into the systemic circulation in two phases (a rapid phase followed by a slow phase).[25] The concentration of the injected solution influences degarelix release from the formed depot (and hence the pharmacokinetic behaviour of the drug).[23-25] Thus, the absolute bioavailability and peak plasma concentration of degarelix tend to decrease with increasing dose concentration, while the terminal elimination half-life ($t_{½\gamma}$) increases.[24,25]
- Degarelix demonstrates linear pharmacokinetics over the dose range of 120–240 mg (at a concentration of 40 mg/mL);[23] there is no evidence of accumulation during repeated administration of the drug (i.e. up to 11–12 maintenance doses).[25]
- In the phase III trial,[21] the maximum plasma concentration (C_{max}) value was 66 ng/mL and the area under the plasma concentration-time curve from day 0 to 28 value was 635 ng • day/mL after subcutaneous administration of a single dose of

degarelix 240 mg (at a concentration of 40 mg/mL); the mean time to C_{max} was 40 hours.[25]

- Mean trough plasma degarelix concentrations in the phase III study[21] were ≈11–12 ng/mL after the initial dose of degarelix 240 mg at a concentration of 40 mg/mL and 11–16 ng/mL after maintenance dosing with degarelix 80 mg at a concentration of 20 mg/mL every 28 days.[25]
- Degarelix binding to plasma proteins *in vitro* is estimated to be ≈90%.[23-25]
- The volume of distribution of degarelix, as evaluated in healthy elderly men, is ≈1 L/kg.[24,25]
- Degarelix undergoes peptide hydrolysis in the hepatobiliary system, resulting in the formation of peptide fragments, which are excreted in the faeces.[23,24] Degarelix metabolites were not detected in the plasma in quantitatively significant amounts following subcutaneous injection of degarelix.[23,25]
- Plasma degarelix levels decline in a biphasic fashion, with a median $t_{½\gamma}$ of ≈43 days after the initial dose, and 28 days after a maintenance dose, according to a population pharmacokinetic model based on the phase III study[21] (results reported in the EU SPC[24] and EMEA report[25]). The long median $t_{½\gamma}$ after subcutaneous administration reflects the very slow release of degarelix from the depot formed at the injection site.[23-25]
- The elimination half-life of degarelix following intravenous administration is ≈17 hours.[26]
- Renal excretion accounts for the elimination of ≈20–30% of a given dose of the drug, which suggests that the hepatobiliary system accounts for excretion of ≈70–80% of the drug.[23-25]
- The clearance of degarelix was 35–50 mL/h/kg following single intravenous doses (0.864–49.4 μg/kg) in healthy elderly men.[24,25]
- Bodyweight and age have a significant impact on the pharmacokinetic properties of degarelix, according to the population pharmacokinetic model based on the phase III study.[25] Degarelix clearance was estimated to increase with weight at a rate of 0.7% per kg, but decrease with age at a rate of 0.6% per year.[25] However, no dose adjustment is proposed[25] or recommended in the EU SPC.[24]
- Degarelix dosage adjustment is not required in the elderly, nor is it necessary in patients with mild or moderate renal or hepatic impairment.[23,25] Only limited data are available on patients with severe renal dysfunction; patients with severe hepatic dysfunction have not been studied. Hence, degarelix should be used with caution in these individuals.[23,25]
- Drug interaction studies have not been performed for degarelix.[23,25] However, it is not a substrate, inducer or inhibitor of the human cytochrome P450 (CYP) system *in vitro*. Therefore, clinically significant CYP-mediated pharmacokinetic drug-drug interactions involving degarelix are unlikely.[23,25]

3. Therapeutic Efficacy

The initial and maintenance doses of degarelix for hormonal therapy of prostate cancer have been identified and evaluated in 1-year, randomized, open-label, multicentre, phase II[19,20] or III[21] trials. The phase II dose-finding studies[19,20] were conducted in Europe[19] or North America;[20] the multinational phase III comparative study[21] used the GnRH agonist leuprolide as the active comparator. These trials have been published in full; additional data from the phase III study that have been presented in preliminary form only[27] are included in the US prescribing information.[23]

These trials enrolled males aged ≥18 years with histologically confirmed prostate cancer (all stages) for whom endocrine treatment (except for neoadjuvant hormonal therapy) was indicated.[19-21] Where stated, patients were required to have a baseline serum testosterone level >1.5[21] or >2.2[19,20] ng/mL, an Eastern Co-operative Oncology Group score of ≤2,[19-21] a baseline serum prostate-specific antigen (PSA) level ≥2 ng/mL[19-21] and current TNM staging (including bone scan) within 3 months prior to the study.[19,20] Previous or current hormonal therapy of prostate cancer was not permitted, except in patients having undergone curative-intent localized therapy in which neoadjuvant or adjuvant hormonal therapy for a maximum of 6 months was accepted[19-21] (discontinued >6[21] or 12[19] months

prior to study inclusion). No other testosterone-modifying drugs were allowed.[19-21] Patients considered to be candidates for curative therapy were excluded.[19-21]

The intent-to-treat (ITT) population was defined as the number of randomized patients who received treatment (n = 127,[20] 187[19] and 610[21]). In terms of the baseline characteristics of the overall ITT study populations, patient age ranged from 72 to 76 years, serum testosterone levels ranged from 3.93 to 4.13 ng/mL and serum PSA levels ranged from 13.4 to 27.6 ng/mL (median values). Among the enrollees, 19–20% had metastatic cancer, 11–32% had locally-advanced disease, 22–43% had local disease and 19–28% were incompletely classifiable.[19-21]

Phase II Dose-Finding Trials

At randomization, patients in the European study[19] received either an initial subcutaneous dose of degarelix 200 or 240 mg followed by maintenance doses of 80, 120 or 160 mg (n = 30–33 per group) every 28 days. In the North American study,[20] patients received an initial dose of degarelix 200 mg followed by maintenance doses of 60 mg (n = 63) or 80 mg (n = 64) every 28 days. All degarelix doses were administered at a concentration of 40 mg/mL, with the exception of the maintenance doses in the North American study (20 mg/mL).[19,20]

With the exception of PSA levels in the European study,[19] baseline characteristics were well matched between the treatment groups in the two trials.[19,20] Median baseline PSA levels ranged from 15.2 ng/mL in the degarelix 200/80 mg group to 35.3 ng/mL in the 240/120 mg group in the European study (median for all treatment groups was 27.6 ng/mL).[19]

Primary[19] or co-primary[20] endpoints were the proportion of patients with testosterone suppression to ≤0.5 ng/mL at all 28-day (monthly) measurements throughout 1 year of treatment (hereafter referred to as a 'treatment response'),[19,20] and the proportion of patients with a treatment response at all monthly measurements throughout 1 year of treatment in only those patients with a treatment response at the 1-month assessment.[20] The primary analysis was performed among 'completers' (i.e. patients who either attended the last visit or had at least one testosterone measurement >0.5 ng/mL between 1 month and 1 year) in the ITT population.[19,20]

Of the 187[19] and 127[20] patients included in the ITT population, 16 (9%)[19] and 16 (13%)[20] were withdrawn due to inadequate testosterone suppression (defined as one testosterone value >1 ng/mL or two consecutive values >0.5 ng/mL after 1 month of treatment and onwards); 147 (79%)[19] and 87 (69%)[20] patients completed the study.

- Degarelix treatment for 1 year resulted in a fast, profound, and sustained suppression of testosterone and PSA, with no evidence of testosterone surge.[19,20]
- Overall, the results suggested that degarelix 240 mg (in preference to 200 mg) was a suitable initial dose, while degarelix 80 mg (in preference to 60 mg) and 160 mg were appropriate maintenance doses.[19,20]
- After 3 days, serum testosterone levels were ≤0.5 ng/mL in 92% and 88% of all patients initially treated with degarelix 240 and 200 mg in the European study,[19] and in 89% of all patients initially treated with degarelix 200 mg in the North American trial.[20]
- After 1 month, testosterone levels were ≤0.5 ng/mL in 95% and 86% of all patients initially treated with degarelix 240 and 200 mg in the European study (p = 0.048),[19] and in 88% of all patients initially treated with degarelix 200 mg in the North American trial.[20]
- Treatment response rates in the European study[19] ranged from 61% (17 of 28 patients) in the degarelix 200/80 mg group to 96% (26 of 27 patients) in the 200/160 mg group. The treatment response rate in the degarelix 240/80 mg group (approved regimen; see section 5) was 90% (27 of 30 patients). Treatment response rates in the North American study[20] were 77% (41 of 53 patients) and 86% (42 of 49 patients) in the degarelix 200/80 mg and 200/60 mg groups, respectively (between-group difference not statistically significant).

- The majority of patients with serum testosterone ≤0.5 ng/mL at the 1-month assessment maintained low levels of testosterone throughout the studies.[19,20] Serum testosterone remained ≤0.5 ng/mL at all subsequent monthly visits in 92% (44/48), 96% (48/50) and 100% (49/49) of patients in the degarelix 80, 120 and 160 mg maintenance dose groups in the European study (pooled data from the initial 200 and 240 mg dose groups),[19] and 93% (42/45) and 98% (41/42) of those in the degarelix 60 and 80 mg maintenance dose groups in the North American study (all patients initially received degarelix 200 mg).[20]

- The median times to 50% and 90% reduction in serum PSA levels were 14 and 56 days, respectively (in all treatment groups in both studies, except the 200/80 mg maintenance dose group in the European study [median time to 90% reduction in PSA was 84 days]).[19,20] The median reduction in PSA relative to baseline was 96–98% after 1 year of treatment with degarelix.[19,20]

- PSA progression (i.e. PSA increase ≥50% from nadir and ≥5 ng/mL on two consecutive visits at least 2 weeks apart) occurred in ≈6–8% of degarelix-treated patients.[19,20] The median time to PSA progression ranged from 140 to 308 days (across all treatment groups in both studies).[19,20]

- Serum levels of DHT, LH and FSH decreased rapidly and remained profoundly suppressed during treatment with subcutaneous degarelix for 1 year.[19,20] The decline in DHT and LH levels was substantial after 1 day and near maximal after 3 days[19,20] (at which time DHT and LH levels were ≤20% and <10% of baseline levels in the European study[19] [values estimated from a graph]). The decline in FSH levels was more gradual (to ≈60%, ≈35%, ≈25% and <15% of baseline levels by days 1, 3, 7 and 14, respectively [values estimated from a graph]).[19]

- The median reductions from baseline in DHT, LH and FSH levels were 83–90%, 92–95% and 74–88%, respectively, at the end of the European study.[19]

Phase III Comparative Study

At randomization, patients received one of three study regimens: an initial subcutaneous dose of degarelix 240 mg (at a dose concentration of 40 mg/mL) followed by maintenance doses of either 80 mg (at a concentration of 20 mg/mL; n = 207) every 28 days or 160 mg (at a concentration of 40 mg/mL; n = 202) every 28 days, or intramuscular injections of leuprolide 7.5 mg every 28 days (n = 201).[21] Flare-protection therapy (oral bicalutamide 50 mg once daily) was administered at the start of leuprolide treatment at the investigator's discretion.

The treatment groups were well matched with respect to baseline characteristics and demographics.[21]

The primary endpoint was treatment response, which was expressed in terms of the Kaplan-Meier estimate of the cumulative probability of testosterone suppression to ≤0.5 ng/mL from day 28 through to day 364.[21] The efficacy of degarelix was assessed using two different criteria: (i) whether the 95% confidence interval (CI) for the treatment response rate was ≥90% (FDA criterion); and (ii) whether degarelix was noninferior to leuprolide with respect to the treatment response rate, using a noninferiority margin (degarelix vs leuprolide) of −10% (EMEA criterion).

- Both degarelix regimens were effective and noninferior to leuprolide in inducing and maintaining testosterone suppression to castrate levels for up to 1 year.[21] Treatment response rates were 97.2% (95% CI 93.5, 98.8) [202 of 207 patients] and 98.3% (95% CI 94.8, 99.4) [199 of 202 patients] in the degarelix 240/80 and 240/160 mg groups, respectively, and 96.4% (95% CI 92.5, 98.2) [194 of 201 patients] in the leuprolide group. Thus, the two degarelix regimens satisfied the predefined criteria for effectiveness and noninferiority with respect to leuprolide.

- Low levels of testosterone were maintained in most patients between days 28 and 354.[21] In the degarelix 240/80 mg, degarelix 240/160 mg and leuprolide groups, four (1.9%), two (1.0%) and six (3.0%) patients, respectively, had inadequate testosterone suppression (i.e. one testosterone value

>1 ng/mL or two consecutive values >0.5 ng/mL between days 28 and 364).

- Degarelix induced testosterone suppression faster than leuprolide (figure 1).[21] After 3 days, median testosterone levels were significantly lower in the degarelix 240/80 mg and 240/160 mg groups than in the leuprolide group (0.24 and 0.26 vs 6.30 ng/mL; both $p < 0.001$).[21] Moreover, at this timepoint, testosterone levels ≤0.5 ng/mL were achieved by >95% of patients in the degarelix 240/80 and 240/160 mg groups compared with none of the patients in the leuprolide group[27] (figure 2).
- By day 28, testosterone levels ≤0.5 ng/mL were achieved by ≥99% of patients in all three treatment groups (figure 2).[21,27] The median testosterone level from day 28 through to day 364 was 0.082, 0.088 and 0.078 ng/mL in the degarelix 240/80 mg, degarelix 240/160 mg and leuprolide groups, respectively.[21]
- Degarelix was not associated with testosterone surges.[21] None of the degarelix recipients experienced an increase in testosterone ≥15% from baseline on any 2 days during the first 2 weeks. In the leuprolide group, 17 (74%) of 23 patients who received concomitant bicalutamide and 144 (81%) of 178 patients who did not receive bicalutamide had a testosterone surge.
- Likewise, degarelix was not associated with testosterone microsurges.[21] On day 255 or 259 of the study (i.e. day 3 or 7 after the ninth injection), none of the degarelix recipients had an increase in testosterone level of >0.25 ng/mL relative to that on day 252 (i.e. the day of the ninth injection). Eight (4%) leuoprolide recipients had an increase of >0.25 ng/mL, with four of these reaching a testosterone level >0.5 ng/mL.
- Degarelix induced PSA suppression more rapidly than leuprolide (figure 1).[21,27] Reductions from baseline in median PSA levels were significantly ($p < 0.001$) lower in the degarelix 240/80 mg and 240/160 mg groups than in the leuprolide group at 14 days (64% and 65% vs 18%) and 28 days (85% and 83% vs 68%) [figure 1].
- The incidences of PSA progression were 8.9%, 14.2% and 14.1% in the degarelix 240/80 mg, degarelix 240/160 mg and leuprolide groups, respectively.[21]

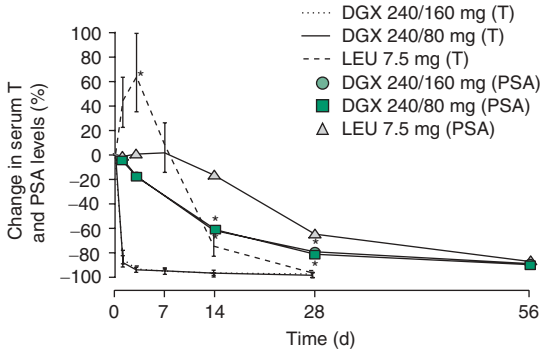


Fig. 1. Comparative effect of degarelix (DGX) and leuprolide (LEU) on serum testosterone (T) and prostate-specific antigen (PSA) levels in patients with histologically confirmed prostate cancer (all stages). Median percent changes in T and PSA levels within the first 56 days among patients who received an initial subcutaneous DGX dose of 240 mg followed by maintenance doses of 80 mg (DGX 240/80 mg; n = 207) or 160 mg (DGX 240/160 mg; n = 202) every 28 days, or intramuscular injections of LEU 7.5 mg every 28 days (n = 201), in a 1-year, randomized, open-label, multinational, phase III study.[21,27] * $p < 0.001$ vs LEU 7.5 mg.

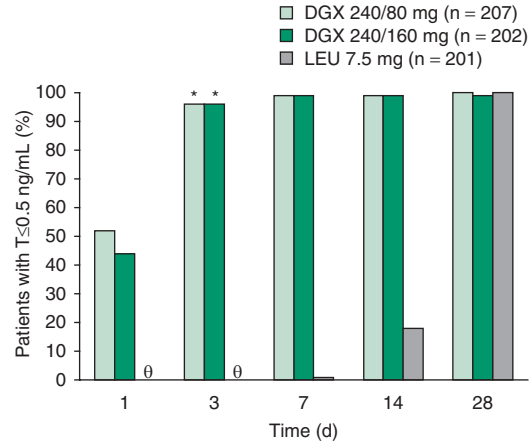


Fig. 2. Comparative effect of degarelix (DGX) and leuprolide (LEU) on serum testosterone (T) levels in patients with histologically confirmed prostate cancer (all stages). Proportion of patients with T ≤0.5 ng/mL within the first 28 days among those who received an initial subcutaneous DGX dose of 240 mg followed by maintenance doses of 80 mg (DGX 240/80 mg) or 160 mg (DGX 240/160 mg) every 28 days, or intramuscular injections of LEU 7.5 mg every 28 days, in a 1-year, randomized, open-label, multinational, phase III study,[21,27] as reported in the US prescribing information.[23] θ indicates zero; * $p < 0.001$ vs LEU 7.5 mg.

• LH and FSH levels decreased immediately after the first subcutaneous dose of degarelix, but increased transiently (before falling) following the initial intramuscular injection of leuprolide;[21] this is consistent with the respective mechanisms of action of these agents. At the end of the study, FSH levels had decreased by ≈89% relative to baseline in degarelix recipients and by 55% relative to baseline in leuprolide recipients.[21]

4. Tolerability

The following tolerability profile of subcutaneous degarelix is based primarily on findings from the phase III study[21] discussed in section 3, and includes data derived from the US prescribing information.[23]

• One year of treatment with subcutaneous degarelix was generally well tolerated.[19-21] The adverse events reported were mostly related to the drug administration route and the negative consequences of androgen deprivation therapy. No apparent dose-dependent adverse events were detected.[19,20]

• In the phase III study,[21] 163 (79%) of 207 patients in the degarelix 240/80 mg group, 167 (83%) of 202 patients in the degarelix 240/160 mg group and 156 (78%) of 201 patients in the leuprolide group reported treatment-emergent adverse events, which were mostly mild to moderate in intensity. Injection-site reactions, hot flushes, ALT increases and weight increases were the most frequent treatment-emergent adverse events in degarelix recipients[23] (table I).

• Pain (28%), erythema (17%), swelling (6%), induration (4%) and nodule (3%) were the most common injection-site reactions reported in patients receiving degarelix 240/80 mg or 240/160 mg.[21,23] These local reactions, which occurred predominantly after the initial dose, were mostly transient, rated mild to moderate in intensity (grade 1 or 2) in ≥98% of patients and resulted in discontinuation in <1% of patients.[23]

• The frequency of some adverse events was significantly different between the pooled degarelix 240/80 mg and 240/160 mg groups and the leuprolide group.[21] Degarelix was associated with significantly higher incidences of injection-site

Table I. Comparative tolerability of degarelix (DGX) and leuprolide (LEU) in patients with histologically confirmed prostate cancer (all stages). Incidence of treatment-emergent adverse events (occurring in ≥5% of patients in any group) in patients who received an initial subcutaneous DGX dose of 240 mg followed by maintenance doses of 80 mg (DGX 240/80 mg; n = 207) or 160 mg (DGX 240/160 mg; n = 202) every 28 days, or intramuscular injections of LEU 7.5 mg every 28 days (n = 201), in a 1-year, randomized, open-label, multicentre, phase III study[21]

Adverse event	No. of patients (%)			
	DGX 240/80 mg	DGX 240/160 mg	pooled DGX 240/160 mg and 240/80 mg	LEU 7.5 mg
Injection-site reaction[a]	35	44	40	<1†
Hot flush	26	26	26	21
ALT increase	10	8	9	5
Weight increase	9	11	10	12
Back pain	6	6	6	8
Hypertension	6	7	6	4
AST increase	5	5	5	3
Arthralgia	5	3	4*	9
Urinary tract infection	5	1	3**	9
Fatigue	3	6	5	6
Hypercholesterolaemia	3	6	5	2
Chills	3	5	4*	0
Constipation	3	5	4	5

a Includes injection-site pain, erythema, swelling, induration and nodule.

* $p < 0.05$, ** $p < 0.01$ vs LEU 7.5 mg; † $p < 0.001$ vs pooled DGX.

reactions and chills, but significantly lower incidences of arthralgia and urinary tract infections, than leuprolide (table I).

- Chills generally occurred 5–10 hours after degarelix administration and lasted for ≤24 hours.[21] Although chills can be indicative of an allergic reaction, no systemic allergic reactions were reported with degarelix in this study.[21]
- Hepatic laboratory abnormalities in degarelix-treated patients were primarily mild to moderate in intensity (grade 1 or 2) in >99% of patients and generally reversible.[23] In the phase III study,[21] 7% of degarelix recipients in the pooled 240/80 mg and 240/160 mg groups compared with 6% of leuprolide recipients had ALT levels of more than 3 times the upper limit of normal (ULN), although none had a concomitant increase in bilirubin of >1.5 × ULN.[21]
- Serious adverse events were reported by 10% and 12% of patients in the degarelix 240/80 mg and 240/160 mg groups, respectively, compared with 14% of patients in the leuprolide group.[21]
- The incidences of adverse events leading to study withdrawal were not significantly different in the three treatment groups: 7%, 9% and 6% in the degarelix 240/80 mg, degarelix 240/160 mg and leuprolide groups, respectively.[21] Five (2%) patients in each of the degarelix groups and nine (4%) patients in the leuprolide group died. None of these deaths were considered to be related to study medication.[21]
- Three (<1%) degarelix recipients in the pooled 240/80 mg and 240/160 mg groups compared with four (2%) leuprolide recipients had a markedly abnormal QT interval corrected for heart rate using Fridericia's formula (QTcF) of ≥500 ms.[21] The median changes from baseline to study end in QTcF were 12.3 and 16.7 msec in the degarelix and leuprolide recipients, respectively.[23]
- Although 10% of patients treated with degarelix for 1 year in clinical trials developed anti-degarelix antibodies, there was no evidence that antibody formation compromised the safety or efficacy of the drug.[23]
- It is anticipated that extended chemical castration with a GnRH antagonist (e.g. degarelix) will lead to a decrease in bone density.[23]

5. Dosage and Administration

Degarelix is indicated for the treatment of (adult male[24]) patients with advanced (hormone dependent[24]) prostate cancer in the US[23] and EU.[24]

The recommended initial dose of subcutaneous degarelix is 240 mg administered in the abdominal region as two injections of 120 mg[23,24] (at a concentration of 40 mg/mL[23]). The recommended maintenance dose is 80 mg administered as a single injection (at a concentration of 20 mg/mL[23]) every 28 days[23] (once per month[24]).

Since long-term androgen deprivation therapy prolongs the QT interval, physicians should consider whether the potential benefits of this form of treatment outweigh the possible risks in patients with congenital long QT syndrome, electrolyte abnormalities or congestive heart failure,[23] those with a history of, or risk factors for, *torsades de pointes*,[24] and those receiving concomitant medicinal products that might prolong the QT interval.[23,24]

Local prescribing information should be consulted for full details of contraindications, warnings, and precautions that relate to the use of degarelix.

6. Degarelix: Current Status

Degarelix has been approved for the treatment of advanced prostate cancer in the US[28] and advanced, hormone-dependent prostate cancer in the EU.[29]

The results of a large phase III trial indicate that the recommended regimen of subcutaneous degarelix is effective, and noninferior to intramuscular leuprolide, in inducing and maintaining testosterone suppression to castrate levels for up to 1 year in patients with prostate cancer. Consistent with the respective mechanisms of action of these agents, degarelix induced testosterone suppression more rapidly than leuprolide, as it did not cause a testosterone surge. Degarelix also induced PSA suppression more rapidly than leuprolide. Degarelix therapy was generally well tolerated.

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