Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Degarelix

Proprietary Product Name: Firmagon

Sponsor: Ferring Pharmaceuticals Pty Ltd

May 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	16 February 2010
Active ingredient(s):	Degarelix
Product Name(s):	Firmagon
Sponsor's Name and Address:	Ferring Pharmaceuticals Pty Ltd PO Box 1014 Gordon NSW 2072
Dose form(s):	Powder for injection with diluent
Strength(s):	80 mg and 120 mg
Container(s):	Vial
Pack size(s):	One or Two Vials with Diluent
Approved Therapeutic use:	Treatment of patients with prostate cancer in whom androgen deprivation therapy is warranted.
Route(s) of administration:	Subcutaneous
Dosage:	240 mg initially (2x 120 mg vials), followed by 80 mg (1x 80 mg vial) at monthly intervals.

Product Background

In Australia, prostate cancer is the second most common cancer in males after non melanoma skin cancer, and the second most common cause of male cancer death after lung cancer [AIHW, 2007]. In 2003, there were 13,526 new cases of prostate cancer and 2,837 deaths due to the disease [AIHW, 2007]. Of the new cases, 84% occurred in men aged 60 years and over, while 84% of the deaths occurred in men aged 70 years and older. The aged-standardised incidence rate was 144.2 [95% confidence interval [CI]: 141.7, 146.6] per 100,000 males, and the age-standardised mortality rate was 34.1 [95% CI: 32.8, 35.4] per 100,000 males. The incidence of prostate cancer increases with age with the rate in 2003 being 86 per 100,000 in men aged 50-54 years and 999 per 100,000 in men aged 85 years and older. In 2003, the risk of diagnosis of prostate cancer was 1 in 9 by age 75, and 1 in 5 by age 85, with the respective figures for risk of death due to prostate cancer being 1 in 84 and 1 in 22. The incidence of new cases of prostate cancer diagnosed in 2003 (144 per 100,000 males) was less than the 1994 peak incidence (184 per 100,000 males) over the period 1982 to 2003.

Degarelix is a third generation gonadotrophin releasing hormone (GnRH) antagonist, which acts through binding to pituitary GnRH receptors. It is a linear decapeptide amide containing seven artificial amino acids, five of which are D-amino acids. The drug produces a rapid decrease in circulating levels of testosterone, luteinising hormone (LH), and follicle stimulation hormone (FSH). The sponsor claims that degarelix has the potential to offer additional therapeutic benefits to those of GnRH agonists for the treatment of patients with prostate cancer as it is not associated with an initial testosterone surge and flare of clinical

symptoms. The initial testosterone surge after treatment with GnRH receptor agonists has been reported to worsen the clinical status of some patients with prostate cancer (for example increased bone pain, spinal cord compression, ureteric obstruction). Australian registered drugs providing androgen deprivation therapy (ADT) for advanced prostate cancer include GnRH agonists (leuprorelin acetate, goserelin acetate) and anti-androgens (nilutamide, bicalutamide, flutamide, cyproterone acetate). The US National Comprehensive Cancer Network (NCCN) guidelines recommend ADT for up to 2 years for patients with prostate cancer considered to be at high risk of recurrence [NCCN, 2007]. Men with clinically localized stage T3a disease, Gleason score 8 to 10, or Prostate Specific Antigen (PSA) levels greater than 20 ng/mL are categorized by the NCCN as being at high risk of recurrence after definitive therapy. Men at very high risk of recurrence are categorized by the NCCN as those with either: (1) clinical stage T3b to T4; or (2) non-localized cancer (any T, N1). The NCCN principles of ADT for prostate cancer are provided in Table 1 and the TNM staging criteria are provided in Table 2.

Table 1: NCCN - Principles of Hormonal Therapy (Androgen Deprivation Therapy – ADT) for Prostate Cancer.

Neoadjuvant ADT for Clinically Localized Disease

- Neoadjuvant ADT for radical prostatectomy is strongly discouraged.
- Giving ADT before, during and/or after radiation prolongs survival in selected radiation managed patients.
- Adjuvant ADT given after completion of primary treatment is not a standard treatment at this time with the exception of selected high risk patients treated with radiation therapy (See PROS-3). In the largest randomized trial to date using antiandrogen bicalutamide alone at high dose (150 mgs), there were indications of a delay in recurrence of disease but no improvement in survival. Longer follow-up is needed
- In one randomized trial, immediate and continuous use of ADT in men with positive nodes following radical prostatectomy resulted in significantly improved overall survival than those with delayed ADT. Therefore, such patients should be considered for immediate ADT.

Timing of ADT for Advanced Disease (PSA recurrence or metastatic disease)

- The timing of ADT for patients whose only evidence of cancer is a rising PSA is influenced by PSA velocity, patient anxiety, and the short and long term side effects of ADT.
- A significant proportion of these patients will ultimately die of their disease; their prognosis is best approximated by the absolute level of PSA, the rate of change in the PSA level (PSA "doubling time"), and the initial stage, grade, and PSA level at the time of definitive therapy.
- Earlier ADT may be better than delayed ADT, although the definitions of early and late (what level of PSA) are controversial. Since the benefit of early ADT is not clear, treatment should be individualized until definitive studies are done. Patients with a short PSA doubling tim (rapid PSA velocity) and an otherwise long life expectancy should be encouraged to consider ADT earlier, unless they regard the side effects as unacceptable.
- Treatment should begin immediately in the presence of tumor-related symptoms or overt metastases (category 1). Earlier ADT will delay th appearance of symptoms and of metastases, but it is not clear whether earlier ADT will prolong survival. The complications of long term ADT have not been adequately documented.

Optimal ADT

- LHRH agonist (medical castration) and bilateral orchiectomy (surgical castration) are equally effective.
- Combined androgen blockade (medical or surgical castration combined with an antiandrogen) provides no proven benefit over castration alone in patients with metastatic disease.
- Antiandrogen therapy should precede or be co-administered with LHRH agonist and be continued in combination for at least 7 days for patients with overt metastases who are at risk of developing symptoms associated with the flare in testosterone with initial LHRH agonist alone.

- Antiandrogen monotherapy appears to be less effective than medical or surgical castration and should not be recommended. The side effects are different but overall less tolerable.
- No clinical data support the use of triple androgen blockade (finasteride or dutasteride with combined androgen blockade).
- Intermittent androgen deprivation therapy is a widely used approach to reduce side effects, but the long term efficacy remains unproven.
- Patients who do not achieve adequate suppression of serum testosterone (less than 50 ng/mL) with medical or surgical castration can be considered for additional hormonal manipulations (with estrogen, antiandrogens, or steroids), although the clinical benefit is not clear.

Secondary Hormonal Therapy

- The androgen receptor remains active in patients whose prostate cancer has recurred during androgen deprivation therapy (castration-recurrent prostate cancer); thus, ADT should be continued.
- A variety of strategies can be employed if initial ADT has failed which may afford clinical benefit, including antiandrogen withdrawal, and administration of antiandrogens, ketoconazole, or estrogens; however, none of these has yet been demonstrated to prolong survival in randomized clinical trials.

Monitor/Surveillance

- Patients being treated with either medical or surgical castration are at risk for having or developing osteoporosis. A baseline bone mineral density study should be considered in this group of patient, especially if longterm ADT is planned.
- Supplementation with calcium (500mg daily) and vitamin D (400 IU) is recommended for all men on long-term ADT.
- Men who are osteopenic/osteoporotic should be strongly considered for bisphosphonate therapy with zoledronic acid, pamidronate, alendronate, raloxifene or toremifene.

Source: NCCN® Practice Guidelines in Oncology – v.2.2007 – Prostate Cancer.

In Australia, there are no GnRH antagonists registered for the treatment or prostate cancer, however, there are drugs of this class registered for the treatment of female infertility (cetrorelix acetate, ganirelix acetate). The GnRH antagonist abarelix (Plenaxis) was approved by the US Food and Drug Administration (FDA) in November 2003 for the treatment of advanced prostate cancer for patients with no alternative treatment options [FDA, 2005]. The indication was restricted because of the risk of serious, and potentially life-threatening, allergic reactions associated with abarelix. Consequently, the drug was not distributed through retail pharmacies but directly to physicians and hospital pharmacies enrolled in the Plenaxis Risk Management Program (RMP). The sponsor of abarelix (Praecis Pharmaceuticals Incorporated) withdrew the drug from US marketing in May 2005 for "commercial considerations".

Table 2: Staging of prostate cancer [CS21].

Localized: T 1/2 and (NX or N0) and M0
Locally advanced: [T 3/4 and (NX or N0) and M0] or [N1 and M0]
Metastatic: M1

PRIMARY TUMOUR (T)

TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
T1 Clinical inapparent tumour not palpable or visible by imaging
- T1a Tumour incidental histologic finding in 5% or less of tissue resected
- T1b Tumour incidental histologic finding in more than 5% of tissue resected
- T1c Tumour identified by needle biopsy (eg. because of elevated PSA)

T2 Tumour confined within prostate[1]
- T2a Tumour involves one lobe
- T2b Tumour involves both lobes

T3 Tumour extends through the prostate capsule
- T3a Extracapsular extension (unilateral or bilateral)
- T3b Tumour invades seminal vesicle(s)

T4 Tumour is fixed or invades adjacent structures other than seminal vesicles, bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

REGIONAL LYMPH NODE (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph-node metastasis
N1 Regional lymph node metastasis

DISTANT METASTASIS (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
- M1a Non-regional lymph nodes
- M1b Bone
- M1c Other sites

There are several GnRH *agonists* registered for the treatment of prostate cancer. These cause initial stimulation of the GnRH receptor, with an initial increase in testosterone release. However, chronic administration results in inhibition of the receptor. Registered GnRH agonists for the treatment of prostate cancer are:

- Leuprorelin - Lucrin (Abbott) and Eligard (Hospira)
- Goserelin - Zoladex(AstraZeneca)
- Triptorelin - Diphereline (Ipsen)

A potential advantage of degarelix over GnRH agonists is the absence of the initial testosterone surge, which may be associated with adverse clinical outcomes.

Regulatory Status

A similar application to the current Australian application for degarelix has been approved in the USA on 24 December 2008, the European Union (EU) on 17 February 2009, Canada on 16 November 2009 and in Mexico and Ukraine.

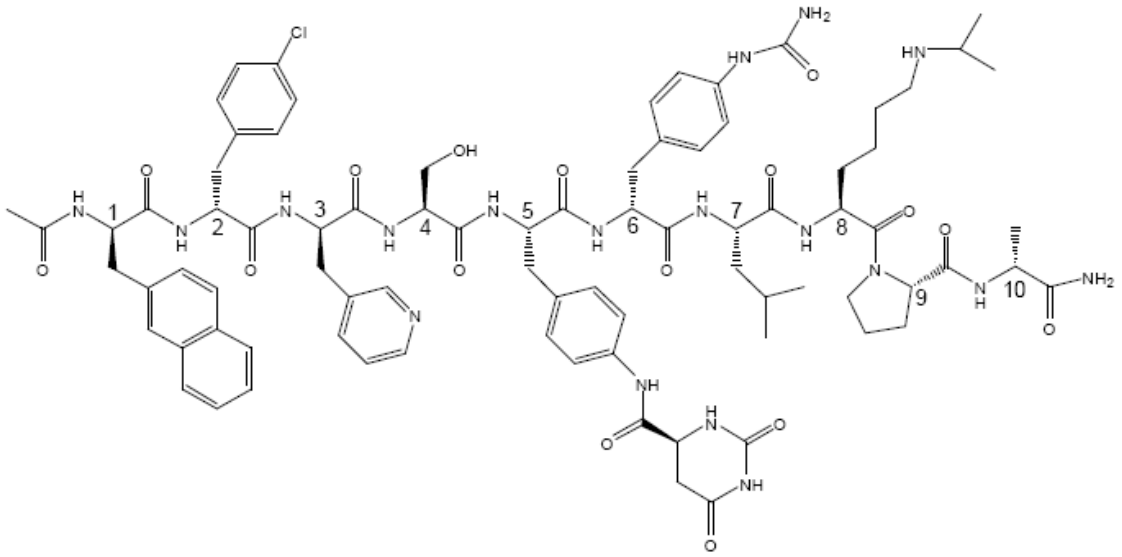
Product Information

The approved product information current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Degarelix is a synthetic gonadotropin-releasing hormone (GnRH) antagonist. (Gonadorelin is pyroGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2). Degarelix is a substituted, linear decapeptide. Degarelix contains seven unnatural (including D) amino acids. It is presented as a single enantiomer. There is no BP/Ph.Eur. or USP monograph.[1]



The drug is made by liquid phase, convergent peptide synthesis. All drug substance manufacturing details were included within the submission.

Drug Product

A key aspect of the proposed Firmagon product is the intrinsic tendency of degarelix to gel at concentrations above about 1 mg/mL. The proposed products are administered as 40 mg/mL or 20 mg/mL solutions. While aqueous solubility of degarelix in water is initially high, the solutions turn turbid or viscous on standing. Thus Ferring describes the reconstituted product as a "suspension". This is attributed to 'fibrillation' (self-aggregation) of the peptide. *In vivo* gelling gives a depot formation "instantaneously" following subcutaneous administration.

Firmagon is a powder for injection; it is administered by abdominal, subcutaneous injection after reconstitution with Water for Injection. A starting dose of 240 mg (administered as 2 x 120 mg) is recommended, followed by a monthly dose of 80 mg.

Ferring proposes registration of both 80 and 120 mg powders for injection. The products are presented with diluent (Water for Injection in a vial), syringes and needles. The starting and monthly doses are administered as different concentration solutions.

The presentation of the diluent is perhaps suboptimal. With the 'starting dose pack', 3.0 mL is taken from each of the two 6 mL diluent vials (remainders discarded). With the 'maintenance dose pack', 4.2 mL is taken from one 6 mL diluent vial.

[1] BP: British Pharmacopoeia, Ph. Eur: European Pharmacopoeia, USP: United States Pharmacopoeia

Bioavailability

Bioavailability data includes a study providing a parallel group estimate of absolute bioavailability after subcutaneous dosing. However, because the dose and the concentration did not match those proposed for registration, the study was not been reviewed by the quality evaluator.

Quality Summary and Conclusions

The application was considered at the November 2009 meeting of the Pharmaceutical Subcommittee (PSC) of the Australian Drug Evaluation Committee (ADEC). No objections to registration were raised.

There were no objections to registration on chemistry, manufacturing or quality control grounds.

III. Nonclinical Findings

Introduction

Ferring Pharmaceuticals Pty Ltd has applied to register Firmagon for the treatment of prostate cancer. Firmagon is the decapeptide, degarelix, which is intended to be administered monthly as a subcutaneous (SC) dose, where it forms a depot for the slow release of degarelix. A comprehensive set of studies was submitted in support of the application. This set included appropriate additional studies to investigate local tolerance and antigenicity, consistent with the chemical nature of degarelix (a peptide) and the intended administration route (SC).

Pharmacology

Primary pharmacodynamics

Degarelix is a gonadotropin releasing hormone (GnRH) receptor antagonist that by inhibiting pituitary gland GnRH receptors prevents the release of luteinising hormone (LH) and subsequently reduces the production of testosterone, which is known to stimulate cell proliferation and prostate cancer. Currently there are no GnRH antagonists approved for use in prostate cancer in Australia. However, the GnRH superagonists, triptorelin, goserelin, leuprorelin, naferelin and buserelin, are approved in Australia for use in prostate cancer. They have a similar mode of action to the GnRH antagonists - to reduce circulating testosterone.

Currently there are two registered GnRH antagonists (cetrorelix and ganirelix) approved for use in Australia, albeit not for the treatment of prostate cancer but for the prevention of premature ovulation in patients undergoing a controlled ovarian stimulation followed by oocyte pickup. Abarelix is a GnRH antagonist that had been approved in the US for use against prostate cancer. Cetrorelix, ganirelix, abarelix and degarelix are all decapeptides similar in sequence, with a similar mode of action. However, cetrorelix and ganirelix do not form slow release depots in the same manner as degarelix.

Three primary indicators of pharmacodynamic efficacy were used: *in vitro* receptor binding studies, *in vivo* effects on plasma testosterone levels and *in vivo* anti-tumour activities. Degarelix was a specific antagonist of the human GnRH receptor with a K_i of 1.68 nM. The inhibition of GnRH receptors was similar with other currently registered GnRH antagonists; the median inhibitory concentration (IC_{50}) for cetrorelix was 4.2 nM, for ganirelix 3.6 nM, for abarelix 3.5 nM and for degarelix 3 nM (Rivier, 2001).

Degarelix was capable of suppressing plasma testosterone concentrations in nonclinical species. Plasma concentrations of degarelix of≥1 ng/mL in rats and ≥5 ng/mL in dogs and

monkeys resulted in undetectable plasma testosterone levels. These plasma levels are similar to cetrorelix and ganirelix plasma concentrations required to suppress testosterone levels, demonstrating both *in vitro* and *in vivo* similarities in efficacy between the three peptides.

Degarelix was tested against three experimental models of prostate cancer: tissue grafts of the androgen-dependent rat prostate tumour Dunning R-3327H, the androgen-dependent human prostate tumour PAC120 and the androgen-independent human prostate tumour PC3. In the two androgen-dependent prostate cancer models, degarelix arrested tumour growth after a latency period of 14 to 21 days. Tumour growth inhibition (TGI) was similar in magnitude with physical castration (average TGI 77% at 1-2 mg/kg every 2 weeks or 1 month SC compared with 75% with physical castration) and was on average better than with the superagonist, triptorelin (average TGI 52%). Long-term animal survival after 3 or 18 months treatment with degarelix was slightly less than with physical castration (73% compared with 91%) but was greater than with the superagonists triptorelin and leuprorelin, where survival rates were similar with untreated controls, even though tumour growth was retarded. The efficacious dose of degarelix used was 1-2 mg/kg/month SC which, based on the area under the plasma concentration time curve (AUC) data from Studies TOX0101 and CAR0101, is below the anticipated clinical exposure of degarelix at the maximum recommended dose (see Table 3).

Secondary pharmacodynamics and safety pharmacology

A standard set of safety pharmacology studies were performed. Overall, the safety profile was largely consistent with other members of the GnRH antagonist class. Though there were some signs of hypersensitivity to external stimuli from 1 mg/kg SC in rats and mice, there was no indication of neurotoxic or neurobehavioural effects with degarelix up to 50 mg/kg SC. These doses corresponded to ≤154 ng/mL plasma degarelix concentrations or up to 3-fold the clinical maximal plasma concentration (C_{max}).

No cardiovascular effects were observed after SC or slow intravenous (IV) infusion of degarelix up to 3 mg/kg in dogs, 50 mg/kg in rats or 50 mg/kg in monkeys. However, consistent with other members of this class, IV (bolus) doses of degarelix resulted in hypotension in several nonclinical species; in monkeys, at doses ≥1.25 mg/kg/day and dogs at 3 mg/kg. These doses resulted in peak plasma concentrations ($C_{5\text{-}15\ min}$) >6363 ng/mL, or >100-fold the clinical C_{max}. The hypotension is suggested to be due to histamine release from mast cells resulting in vasodilation and appears to be a consistent phenomenon across the GnRH antagonist class (Doehn *et al.*, 2006; Rivier *et al.*, 1992). There was evidence of histamine release *in vivo* in dogs as well as in *in vitro* studies. Degarelix had a lower histamine releasing potential than cetrorelix, ganirelix or abarelix. Though the recommended SC dose of degarelix is about 1000-fold greater than cetrorelix and ganirelix (240 mg compared with 0.25 mg), this results in only a 5-10 fold (based on C_{max}) or 13-24 fold (based on AUC) higher systemic exposure than cetrorelix or ganirelix (Table 3).

Table 3: Comparison of AUC and Cmax of degarelix with other currently registered GnRH antagonists.

	Dose	$AUC_{0\text{-}24h}$ (ng.h/mL)	Cmax (ng/mL)	Reference
Cetrorelix	0.25 mg/day	44.5	6.4	Duijkers *et al.* (1998)
Ganirelix	0.25 mg/day	77.1	11.1	US FDA PI
Degarelix	240 mg	1060[a]	53.4	Study CS21

[a] *Based on $AUC_{0\text{-}4\ weeks}$ 29.8 μg.h/mL*

Abarelix was registered in the US in 2003 for use in prostate cancer. It was withdrawn in 2005 due to complications associated with immediate-onset allergic reactions. There is some evidence to suggest that degarelix has a lower potential to release histamine than abarelix: the reduced solubility of degarelix should correlate with reduced histamine release potential (Rivier *et al.*, 1992; Haviv *et al.*, 1993) and there was no evidence of hypotension associated with histamine release in nonclinical toxicity studies at plasma concentrations up to 42-fold the clinical C_{max}. However, due to species differences in the response of mast cells to various factors, the histamine releasing potential with subsequent systemic effects of degarelix will ultimately rely on clinical data.

There were no effects on renal or gastrointestinal (GI) function up to 3 mg/kg SC in rats. This dose was relatively low, resulting in a C_{max} approximately 2-fold the anticipated clinical C_{max}, and therefore potential renal and GI effects were not adequately assessed in these studies. Some indicators of effects on the renal system were observed in repeat-dose toxicity studies at higher concentrations. These effects are discussed in more detail below (*General toxicity*). There were no effects on GI function in repeat-dose toxicity studies at exposures up to 9-fold the clinical exposure.

Pharmacokinetics

The bioavailability of SC administered degarelix was 60-91% in rats and dogs at 30 µg/kg and 3 µg/kg, respectively. The relative bioavailability of degarelix decreased with increasing dose concentration (Agersø *et al.*, 2003). This was suggested to be due to a concentration-dependent increase in the rigidity of the gel in the depot, making it less available.

Both the time to maximal plasma concentration (T_{max}) and apparent elimination half-life appeared to increase with higher SC doses of degarelix. These pharmacokinetic profiles are consistent with "flip-flop" kinetics, where the absorption is rate-limiting and affects the apparent rate of elimination. This type of kinetics is commonly observed in slow release drug models (Boxenbaum, 1998). The slow-release profile of degarelix resulted in apparent accumulation in repeat SC dose studies in rats when treated fortnightly. No apparent accumulation was observed in monkeys treated monthly.

Flip-flop kinetics were not observed with ganirelix or cetrorelix (Duijkers *et al.*, 1998). This is most likely due to the relatively low clinical dose of cetrorelix and ganirelix (0.25 mg/day) compared with degarelix (240 mg single dose) which would be at a level below which gel formation would occur. The higher dose (about 1000 fold) of degarelix results in a 13-24 fold greater systemic exposure (based on AUC) than cetrorelix or ganirelix (see Table 3) which should be taken into account with toxicological comparisons between these members.

Plasma protein binding was similar in the plasma of rats, mice, monkeys, dogs and humans (86-93%). There was no evidence of concentration-dependent binding. The tissue distribution pattern of degarelix was fairly consistent with other members of the class with highest concentrations observed in the organs of excretion (liver, bile, small intestine, large intestine, kidney, urinary bladder), some organs of the endocrine system (adrenals, pituitary, thyroid), reproductive organs (ovaries, uterus, prostate, testes, epididymides), organs rich in reticuloendothelial cells (lungs, aorta, vena cava, thymus, spleen, bone marrow), the lacrimal glands and the injection site after SC administration. No significant difference in tissue distribution was observed between rats, dogs and monkeys.

Degarelix is similar in sequence to cetrorelix and ganirelix and the metabolic degradation of degarelix appeared to be similar to these registered GnRH antagonists. There was little degradation of degarelix by cytochrome P450 (CYP450) enzymes or through glucuronidation and metabolism occurred primarily through proteolytic cleavage. Due to slight differences in

peptide sequence, different proteolytic cleavage patterns were observed between degarelix, cetrorelix and ganirelix.

The metabolism of degarelix was similar in all species (rats, dogs, monkeys and humans) with unchanged degarelix as the main component of plasma and urine and truncated peptides as the main component of drug-related material in bile and faeces. The excretion of degarelix-associated material occurred approximately equivalently through urinary and faecal routes in rats and dogs but only 20% of degarelix-associated material was excreted through the urinary route in monkeys and humans. Based on pharmacokinetic profiles, rats and monkeys, which were used in the repeat-dose toxicity studies, were suitable nonclinical models.

Relative exposure

Due to the slow release formulation of degarelix, increased AUC and C_{max} values were observed in repeat dose studies of fortnightly SC administration of degarelix to rats. For comparative purposes, the average of data for AUC and C_{max} from all doses was used. AUC data were converted to the area under the concentration plasma time curve from time zero to 4 weeks ($AUC_{0\text{-}4\ weeks}$) when compared with clinical data ($AUC_{0\text{-}4\ weeks}$ of 29.8 µg.h/mL (1240 ng.day/mL) and C_{max} of 53.4 ng/mL; Tables 4 and 5).

In the sponsor's Nonclinical Overview, exposure ratios were determined by comparing the C_{mean} ($AUC_{0\text{-}t}/t$) achieved in nonclinical studies with that achieved clinically. Calculations by this method would result in the same exposure ratios as in Table 4. The values in Table 4 differ from those in the sponsor's Nonclinical Overview as data from a 240 mg dose at 40 mg/mL were used rather than data for the 80 mg dose at 20 mg/mL (maintenance) dose which was used in the Nonclinical Overview. As a consequence, the ratios were about 2-fold lower in Table 4 compared with the Nonclinical Overview.

With administration according to the proposed clinical route (SC), maximum AUC exposures achieved in nonclinical studies were up to 9-fold the anticipated clinical systemic exposure. It is unlikely higher exposures would have been possible due to limitations in absorption after an SC dose. Due to complications associated with high peak plasma concentrations in IV studies, the doses used were close to the maximum tolerated IV dose.

Table 4: Pharmacokinetic/toxicokinetic data from relevant SC studies.

Species/Study No.	Study duration	Doses (mg/kg/2 weeks)	$AUC_{0\text{-}4\ weeks}$ (µg.h/mL)	AUC ratio	C_{max} (ng/mL)	C_{max} ratio
Mice						
TOX0111	13 weeks	1, 10, 100	6, 36, 238[a]	0.2, 1.2, 8	261, 404, 2268	5, 8, 42
CAR0102	104 weeks	2, 10, 50	16, 74, 272[a]	0.5, 2.5, 9	398, 544, 1217	7.5, 10, 23
Rats						
TOX0112	13 weeks	0.5, 5, 50	4, 23, 82[a]	0.1,1, 3	87, 132, 261	2, 2.5, 5
TOX0101[b]	26 weeks	0.5, 2, 10	8, 19, 66[a]	0.3, 0.6, 2	62, 85, 152	1, 1.6, 3
TOX0401	26 weeks	10, 50, 100	56, 149, 198[a]	2, 5, 7	254, 447, 506	5, 8, 9
CAR0101	104 weeks	2, 10, 25	29, 100, 197[a]	1, 3, 7	155, 301, 534	3, 6, 10
Monkeys						
TOX0126	12 months	0.5, 5, 50	7, 37, 212	0.2, 1.2, 7	63, 166, 1204	1, 3, 23

[a]Original data from Studies TOX0111, CAR0102, TOX0101, TOX0112, TOX0401 and TOX0101 were multiplied by 2 to convert to $AUC_{0\text{-}4\ weeks}$; [b]Data available for dose 13 only.

Table 5: Pharmacokinetic/toxicokinetic data from relevant IV studies. No Observable Effect Levels (NOELs) are shown in **bold-face**.

Species/Study No.	Study duration	Doses (mg/kg/day)	$C_{5\ min}$ (ng/mL)	C_{max} ratio
Rats				
TOX0109	2 weeks	**0.05**, 0.35, 2.5	**136**, 1232, 10148	**3**, 23, 190
TOX0122	4 weeks	0.03, 0.3, 3	89, 1130, 7027	2, 21, 132
Monkeys				
TOX0115	2 weeks	0.025, **0.175**, 1.25	226, **1506**, 8513	4, **28**, 159
TOX0120	4 weeks	0.25, 0.8, 2.5	1893, 4528[a], 6363[b]	35, 85, 119

[a]$C_{10\ min}$; [b]$C_{15\ min}$

Toxicology

General toxicity

Though both sexes were examined in toxicity studies, for the purpose of the intended indication in the current application (prostate cancer), only male-specific toxicities are discussed below.

Acute toxicity

In several bolus IV nonclinical studies, death occurred either during administration or within 30 min. after injection. This was observed in mice at 100 mg/kg and rats at≥60 mg/kg. The mechanism of instantaneous death was not elucidated but it may have been as a result of the extreme hypotension (see *Safety Pharmacology*) leading to cardiac failure or due to the deposition of degarelix in lung and heart tissue resulting in thrombosis. Abnormal respiration and respiratory distress were also observed after bolus IV administration and may be a symptom of hypotension. As these occurred at plasma concentrations significantly greater than the clinical C_{max}, they are unlikely to be of clinical concern.

Toxicological effects associated with pharmacological action

Toxicological effects observed were typical of those seen in response to androgen deprivation therapy. These included decreased body weights, atrophy of the reproductive organs (testes, epididymides, prostate, seminiferous tubules) with associated oligospermia, increased adrenal and thymic weights, decreased kidney and liver weights, transient decreases in red blood cell parameters, increases in white blood cells, prolonged prothrombin time (PTT), decreased activated partial thromboplastin time (APTT), clinical chemistry changes (increased alkaline phosphate (ALP), cholesterol and triglycerides) and bone marrow effects (granulopoiesis and arteritis) (Yannucci *et al.*, 2006; Nishiyama *et al.*, 2005; Aydilek and Aksakal, 2005; Smith *et al.*, 2001; Pinski *et al.*, 1993; Uchida *et al.*, 1985). Though a NOEL for these effects could not be determined, they were expected with this type of treatment and are not of toxicological concern.

Toxicological effects following SC administration

Aside from the expected pharmacological effects, no target organ toxicity was observed after SC administration. The main concern of clinical relevance was the local reaction at the injection site which was on occasions the reason for premature euthanasia at high doses (≥50 mg/kg/2 weeks to rats and mice, compared with 4.8 mg/kg/month clinical dose[2]). This is discussed further in *Local tolerance.*

Toxicological effects following IV administration

Aside from pharmacological effects associated with GnRH antagonism, transient effects on blood pressure and heart rates were observed as were systemic toxic effects in the lungs, kidneys and liver of rats and the kidneys and liver of monkeys, after IV administration of degarelix. The transient effects on cardiovascular parameters are discussed above in *Secondary pharmacodynamics and safety pharmacology.*

Eosinophilic and granuloma formation were observed in the lungs as well as other organs of the reticuloendothelial system of rats treated with 3 mg/kg/day IV degarelix for 4 weeks. Whilst no histopathological effects were observed in the liver of IV-treated rats, degarelix precipitates were identified in swollen Kupffer cells in monkeys treated with ≥0.8 mg/kg/day IV degarelix. Granular degarelix was also observed in tubular cells of the kidney of monkeys treated with ≥0.25 mg/kg/day IV degarelix. Only in the kidneys were adverse effects observed, with subacute interstitial inflammation and regenerative basophilic tubules of the kidneys in monkeys treated with 0.25 mg/kg/day and tubular degeneration, tubular dilation and peritubular fibrosis in the kidneys of rats treated with≥0.25 mg/kg/day IV degarelix.

Based on tissue distribution data, degarelix localises to the reticuloendothelial system as well as the kidneys and the liver and the effects observed after IV administration of degarelix are most likely related to low solubility and subsequent deposition and precipitation at high concentrations (≥35-fold and ≥132-fold the clinical plasma concentration for monkeys and rats, respectively). Whilst these effects were observed at low doses, they are not clinically-relevant for the proposed SC administration route, where plasma concentrations are likely to be lower due to limitations in absorption from the SC injection site. However, as these effects as well as instantaneous deaths, possibly as a result of deposition in heart and lung tissue, were observed after IV administration, sufficient warnings should be placed in the product information (PI) document to reduce the likelihood of accidental IV administration.

[2] A 240 mg SC dose to a 50 kg individual.

Genotoxicity and carcinogenicity

The potential genotoxicity of degarelix was investigated in the standard battery of tests conducted in accordance with ICH guidelines. All assays were appropriately validated. Consistent with other members of the class (ganirelix, cetrorelix and abarelix), degarelix was not mutagenic or clastogenic. Two rodent carcinogenicity studies were performed with degarelix with maximum SC doses resulting in at least 7-fold the clinical AUC. An increase in hepatocellular adenomas was observed in female mice at all doses of degarelix tested (exposure ratio $[ER]_{AUC} \geq 0.5$), most likely as a result of reduced oestrogen. Haemangiosarcoma incidence in the mesenteric lymph node of female rats was increased at 25 mg/kg/2 weeks ($ER_{AUC}=7$). As there were no neoplastic changes in males of either species, and, considering the mechanism of tumour formation in females and the relatively high exposure ratio for the latter tumour, there are no clinically-relevant carcinogenic concerns for the proposed indication.

This is in contrast to the GnRH agonists that are currently registered for use in prostate cancer. Carcinogenicity studies of leuprorelin, triptorelin, goserelin and nafarelin revealed a high incidence of pituitary adenomas in rodents after prolonged administration (Product information for the respective agents). It is notable that these pituitary tumours from GnRH agonists appear to be clinically relevant (Hands *et al.*, 2007; Massoud *et al.*, 2006). Pituitary adenomas have also been reported after physical castration (Griesbach and Purves, 1960). Feedback stimulation of GnRH release due to low testosterone levels results in the stimulation of pituitary gland GnRH receptors, which does not occur with GnRH antagonists. Therefore the mechanisms of pituitary gland adenoma formation from physical castration and GnRH agonists are likely to be similar, that is, due to over-stimulation of pituitary gland GnRH receptors. This would not occur with GnRH antagonists.

Hyperplasia of the intermediate lobe in pituitary glands in treated male mice in the 104 week carcinogenicity study was observed (NOEL < 2 mg/kg/2 weeks, $ER_{AUC} < 0.5$). An expert opinion stated that this was due to the pharmacological action of degarelix resulting in low LH levels and subsequent over-production of ACTH (Adrenocorticotropic hormone, the main adrenal glucocorticoid stimulating hormone) in the pituitary. However, ACTH is predominantly secreted by the *anterior* lobe of the pituitary and anti-ACTH staining showed no difference between control and treated mice, so this is unlikely to be the mechanism. Therefore, it is unclear if this finding is clinically relevant. LH receptors are known to be expressed in human adrenal glands (Pabon *et al.*, 1996) and GnRH agonists have been used to treat LH-dependent adrenocortical hyperfunction (Lacroix *et al.*, 1999). However, differences in glucocorticoid production and regulation between mice and humans (Kero *et al.*, 2000) may suggest these findings are restricted to mice. In support of this, no pituitary gland histopathological findings were observed in cynomolgus monkeys treated for 12 months ($ER_{AUC} = 7$) or in rats treated for 2 years ($ER_{AUC} = 7$) and no pituitary tumours were observed in carcinogenicity studies in mice and rats treated with abarelix. Therefore GnRH antagonists appear to be less prone to inducing pituitary adenoma formation than GnRH agonists currently registered for treatment against prostate cancer.

Reproductive toxicity

Overall the effects of degarelix on the reproductive system were consistent with other members of the class. Atrophy of male reproductive organs with associated oligospermia was a consistent finding in nonclinical repeat-dose toxicity studies. This was attributed to reduced testosterone levels resulting in reduced libido and male infertility. A NOEL on male fertility of 0.003 mg/kg/day SC degarelix in rats was determined in a preliminary dose-ranging study with small animal numbers (*n*=10 males/group). The infertility was reversible but only several weeks after the final dose, when the plasma degarelix concentrations were below the limit of detection. It was noted that a single male given a single dose of 1 mg/kg SC remained infertile at the end of the study.

A slight increase in pre-implantation loss was observed in untreated females that had successfully paired with treated males. This may be associated with poor sperm quality or seminal transfer of degarelix affecting the female reproductive system, but it did appear to reverse after a sufficient recovery phase.

In treated females, oestrous cycling was disrupted and as a consequence the time to mating was increased. The NOEL for female fertility was 0.03 mg/kg SC degarelix. In embryofetal studies in rats and rabbits, an increase in post-implantation loss, embryofetal deaths, abortions and premature deliveries was observed. The NOEL for these findings was dependent on the time of administration during gestation, with a NOEL of 0.03 mg/kg/day SC in rats if administered after gestation day (GD) 12 but 0.003 mg/kg/day SC if administered GD 6-12. Similarly in rabbits, the NOEL for embryofetal toxicity was 0.001 mg/kg/day SC from GD 6-14 and 0.003 mg/kg/day SC from GD 15-27. Unfortunately, no toxicokinetic data were obtained but based on body surface area, doses used were ≤10% and ≤2% of the clinical dose for rats and rabbits, respectively[3]. Degarelix treatment during the latter stages of pregnancy increased the parturition duration in rats; a NOEL could not be established. No significant effects on postnatal development were observed with maternal treatments up to 0.03 mg/kg/day SC (GD 13-LD 20) in rats. These reproductive effects are not relevant to the proposed indication but need to be considered if future indications in females are proposed.

Local tolerance

Degarelix forms a self-generated depot following SC administration. Granulomatous inflammatory reactions were consistently observed after SC administration in nonclinical studies. The local reaction was considered to be a normal foreign body response. Similar local reactions with haemorrhage, inflammation and granuloma formation have been observed for other slow release depot reagents. The histological observations confirmed this assumption by the extensive presence of macrophages at doses >10 mg/kg in rats. There was no evidence of fibrosis or necrosis which would indicate significant tissue damage at up to 80 mg/mL or 60 mg/animal.

Whilst the local reactions observed were typical of a foreign body reaction to the SC depot, it should be noted that severe local reactions were observed in nonclinical studies after SC administration of high doses of degarelix (≥50 mg/kg/2 weeks at ≥10 mg/mL) and necessitated sacrifice prior to scheduled termination. Furthermore, 2 years after a single 10 or 15 mg SC injection in rats, macrophage aggregation and about 8% of the parent drug substance with peptidic breakdown products were still present, suggesting the local depot and inflammatory responses are long-lived.

[3] Based on a 240 mg dose to a 50 kg individual for 28 days (0.172 mg/kg/day) and mg/kg to mg/m^2 conversion factors of 6 for rats, 15 for rabbits and 33 for humans

Degarelix appeared to be well tolerated after IV and IM injection in rats, and IV, IM, intra-arterial and perivenous injections in rabbits.

Antigenicity

There was no evidence that degarelix stimulated an acute systemic anaphylactic response or passive cutaneous anaphylactic response after SC induction. No detectable antibodies were produced in rats that had been treated with degarelix (up to 100 mg/kg SC). There were no indirect signs of humoral or cell-mediated immunity in the long term repeat-dose toxicity studies. Degarelix does not appear to pose an allergenic risk associated with an immunological response. However, consistent with other members of the GnRH antagonist class and the reason for market withdrawal of some of them, degarelix has the potential to release histamine in mast cells (see *Secondary pharmacodynamics and safety pharmacology*) and this is the main allergic reaction concern.

Impurities

A threshold of ≥0.5% is proposed for a number of impurities in either the active ingredient or the drug product of degarelix. Based on submitted repeat-dose toxicity studies with dose ratios based on body surface area (BSA) of ≥2, the proposed limits have been toxicologically qualified.

Nonclinical Summary and Conclusions

Degarelix was an antagonist of the human GnRH receptor with a K_i of 1.68 nM and was capable of suppressing plasma testosterone concentrations in nonclinical species. In two androgen-dependent prostate cancer models, degarelix arrested tumour growth after a latency period of 14 to 21 days.

A standard set of safety pharmacology studies were performed. Overall, the safety profile was largely consistent with other members of the GnRH antagonist class. Degarelix has the propensity to release histamine but at a similar level to currently-registered GnRH antagonists.

Degarelix displayed “flip-flop” kinetics after SC administration with rate-limiting absorption affecting apparent elimination rates. The relative bioavailability was inversely proportional to dose concentration. Radiolabelled tissue distribution studies demonstrated degarelix partitioned to the organs of excretion, some organs of the endocrine system, reproductive organs and organs rich in reticuloendothelial cells.

The metabolism of degarelix was similar in all species (rats, dogs, monkeys and humans) with unchanged degarelix as the main component of plasma and urine and truncated peptides as the main component of drug-related material in bile and faeces. There was little degradation of degarelix by CYP450 enzymes or through glucuronidation.

Instantaneous death occurred during or shortly after bolus IV dosing in mice at 100 mg/kg and rats at ≥ 60 mg/kg as a result of either extreme hypotension leading to cardiac failure or due to the deposition of degarelix in lung and heart tissue resulting in thrombosis. These occurred at plasma concentrations significantly greater than the clinical C_{max} and are unlikely to be of clinical concern for the current application. Unscheduled sacrifices in the SC studies were related to adverse local reactions.

Aside from injection site reactions, the only toxicological effects observed after SC administration at all doses resulting in sufficiently high systemic exposures were typical of those seen in response to androgen deprivation therapy and were expected with this type of treatment. These included atrophy of the reproductive organs and secondary effects on body weight, haematological and clinical chemistry parameters.

Toxicological effects following IV administration included haemodynamic effects (hypotension) and systemic toxic effects in the lungs, kidneys and liver. These are probably related to low solubility of the drug and subsequent deposition and precipitation at high concentrations (≥35-fold and ≥132-fold the clinical plasma concentration for monkeys and rats, respectively). Though these findings are not clinically-relevant for the proposed SC administration route, they highlight the toxicological concerns associated with inadvertent IV administration.

The potential genotoxicity of degarelix was investigated in the standard battery of tests conducted in accordance with ICH guidelines. Degarelix was not mutagenic or clastogenic. No neoplastic changes were observed in male animals in two rodent carcinogenicity studies at SC doses resulting in at least 7-fold the clinical AUC. However, there were treatment-related increases in the incidence of hepatocellular adenomas in female mice and haemangiosaroma in the mesenteric lymph node of female rats at ≥0.5 and 7 -fold the clinical AUC, respectively. These are not considered clinically-relevant for the proposed indication.

Degarelix treatment resulted in atrophy of the male reproductive organs associated with oligospermia and subsequent infertility. These effects were expected due to the pharmacological action of degarelix. Male infertility was reversible after a sufficient recovery period.

Granulomatous inflammatory reactions in the skin were consistently observed after SC administration in nonclinical studies and were considered to be a normal foreign body response. Severe local reactions were observed only at high doses (≥50 mg/kg for 2 or 4 weeks at ≥10 mg/mL) and necessitated sacrifice prior to scheduled termination. There was no evidence of fibrosis or necrosis which would indicate significant tissue damage at up to 80 mg/mL or 160 mg/animal.

There was no evidence that degarelix stimulated an acute systemic anaphylactic response or passive cutaneous anaphylactic response after SC induction in guinea pigs. However, degarelix has the potential to release histamine and this is the main allergic reaction concern. No detectable antibodies were produced in degarelix-treated rats.

The majority of toxicological effects observed in nonclinical studies with degarelix were associated with its pharmacological action. The only clinically-relevant concern was associated with injection site local reaction severity which can be addressed by clinical data. Degarelix has been extensively and adequately assessed in nonclinical studies and based on the findings reported there are no objections on nonclinical grounds to the registration of degarelix. However, any future extension of indications or difference in administration route for degarelix will require a re-assessment of the nonclinical data and a revision of the PI document.

IV. Clinical Findings

Introduction

The clinical studies were carried out according to the ethical and scientific principles of the Declaration of Helsinki and Good Clinical Practice (GCP). The clinical studies were also undertaken in accordance with relevant national and/or local ethics committee requirements relating to approval and supervision of clinical trials.

The submission included data on 1836 patients with prostate cancer treated with degarelix. The patients with prostate cancer in the clinical studies are considered to be a satisfactory sample of patients in the general population for whom the drug is intended. The submission included 21 studies relevant to the proposed indication including 17 clinical Phase II/III

studies in patients with prostate cancer, 3 Phase I clinical pharmacology studies in healthy volunteers and 1 Phase I study in hepatically impaired patients. The submission included 2 clinical studies in female subjects. These two studies have not been evaluated as they are considered to be unrelated to the proposed indication.

The seventeen clinical studies in patients with prostate cancer included one pivotal Phase III study [CS21] and four supportive Phase II studies [CS07, CS12, CS14, CS15]. All the clinical studies were open-labelled and only the pivotal study included a control group (active control leuprolide). The primary efficacy endpoint in all studies was a biochemical surrogate endpoint: reduction in serum testosterone concentration to castration levels ($\leq$ 0.5 ng/mL). The primary prostate cancer inclusion criteria were similar in all Phase II/III studies. Inclusion criteria included histologically confirmed (Gleason graded) adenocarcinoma of the prostate (any stage). In addition, patients with a rising prostate specific antigen (PSA) level who had previously undergone prostatectomy or radiotherapy with curative intent were eligible for inclusion. Patients were required to have a baseline PSA of $\geq$ 2 ng/mL, except for the first prostate cancer study [CS02] in which the PSA had to be $\geq$ 20 ng/mL.

The seventeen clinical studies are outlined as follows:

One pivotal, Phase III open-label, active-controlled clinical efficacy and safety study which compared the effect on testosterone suppression of two SC degarelix dosing regimens (240 mg starting dose followed by 80 mg or 160 mg maintenance dose every 28 days) with intramuscular (IM) leuprolide 7.5 mg every 28 days [CS21].

Six Phase II, open-label, uncontrolled studies [CS02, CS06, CS07, CS11, CS12, CS14]. Of these six studies, three were considered to provide supportive efficacy data [CS07, CS12, CS14], while three were considered not to be directly relevant to the submission as the dosing regimens were different from that being proposed [CS02, CS06, CS11].

The seven extension studies [CS02A, CS06A, CS07A, CS11A, CS12A, CS14A, CS21A] were designed to examine the long-term (> 12 month) safety of degarelix. Studies CS11A, CS12A, CS14A and CS21A are ongoing and safety data are available from these studies and have been reviewed.

Studies CS02A, CS06A, and CS07A were discontinued as the dosage regimens in these studies did not provide adequate long-term testosterone suppression.

There were three, Phase II, open-label, uncontrolled studies investigating a three-month dosing regimen [CS15, CS15A, CS18]. The starting dose in study CS15 was the same as that being proposed for registration. Consequently, this aspect of the study has been evaluated and the study is considered to be supportive. Studies CS15A and CS18 are on-going.

In addition to the seventeen clinical studies in patients with prostate cancer, the submission also included three clinical pharmacology studies in healthy male volunteers [CS01, CS05, CS06] and one clinical pharmacology study in male patients with hepatic impairment [CS23]. These four studies have been evaluated.

The submission also included two population pharmacokinetic (PPK) studies integrating data from a number of Phase II/III studies in patients with prostate cancer. There were no pharmacokinetic (PK) drug-drug interaction clinical studies, but the submission included four *in vitro* studies which investigated the metabolism of degarelix and its potential for drug-drug interactions. There was a comprehensive sponsor's Integrated Summary of Clinical Safety relevant to patients with prostate cancer. There was also the sponsor's Integrated Summary of Clinical Efficacy which included a *post hoc* analysis of relevant efficacy studies, and a

comprehensive written summary of the clinical pharmacology studies. The submission also included synopses and tabulated summaries of all Phase I/II/III studies.

Pharmacodynamics

The effect of degarelix on suppressing serum testosterone concentration to castration levels (≤ 0.5 ng/mL) was the primary efficacy endpoint for the Phase II/III clinical studies. The secondary endpoints for these studies included additional pharmacodynamic parameters for testosterone as well as pharmacodynamic parameters relating to serum 5-α-dihydrotestosterone (DHT), luteinising hormone (LH), follicle stimulating hormone (FSH), prostate specific antigen (PSA), sex hormone binding globulin (SHBG) and free androgen index (FAI). Consequently, as the primary and secondary efficacy endpoints were almost exclusively pharmacodynamic they have been considered under the efficacy section of this AusPAR. Exploratory analyses of change in serum testosterone concentration and other pharmacodynamic parameters after SC, IM, and IV degarelix were investigated in healthy male subjects [CS01, CS05, CS08]. However, none of the IV, SC, or IM degarelix doses used in healthy subjects were those being proposed for registration. In addition, the mean age of healthy subjects treated with SC degarelix in *studies CS01* and *CS05* was lower than that of patients in the prostate cancer studies. The results from *study CS01* suggested a dose-response relationship for both the extent and duration of testosterone suppression after SC administration. In addition, IV and IM administration were also effective in rapidly suppressing serum testosterone levels [CS05, CS08]. No surge in testosterone levels was observed after SC, IM or IV degarelix. The studies in healthy male subjects demonstrated that degarelix effectively lowered serum testosterone concentration and was a suitable drug for Phase II/III evaluation in patients with prostate cancer.

Pharmacokinetics

There were three Phase I studies which included PK data in healthy men, but none of these used the SC degarelix treatment regimen proposed for registration [CS01, CS05, CS08]. The sponsor nominated *study CS05* as the bioavailability study. It included absolute bioavailability estimates for degarelix after both SC and IM administration. There was one PK study in patients with hepatic impairment [CS23]. There were a number of studies in patients with prostate cancer that included PK data [CS06/6A, CS07/7A, CS12/12A, CS14/14A, CS15, CS21]. The data from *studies CS06* and *CS07* were comprehensive and have been separately evaluated. The data on degarelix plasma concentration from the *pivotal study CS21* has also been reviewed. There were also two population pharmacokinetic (PPK) studies in patients with prostate cancer: one included SC data from studies *CS06/6A*, *CS07/7A*, *CS12/12A*, *CS14/14A*, and *CS15* in prostate cancer and IV data from *study CS05* in healthy subjects; and one included SC data from the pivotal efficacy and safety *study CS21* and IV data from *study CS08* in healthy subjects.

The clinical development program used a validated radioimmunoassay (RIA) method to measure plasma degarelix in the first in-human study [CS01]. In subsequent studies, validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods were used to measure degarelix concentrations in plasma, urine and faeces. The lower-limit of quantification (LLOQ) in the LC-MS/MS human assays was 0.5 ng/mL in plasma and 5 ng/mL in urine. Human serum testosterone concentrations were measured by validated RIA and LC-MS/MS methods. The LC-MS/MS methods had LLOQs for serum testosterone ranging from 30-100 pg/mL depending on the laboratory undertaking the assay.

Formulation

The initial degarelix formulation used in the clinical development program was manufactured using a Solid Phase Peptide Synthesis (SPPS) method. The SPPS formulation was used in

Phase I/II studies *CS01, CS05, CS08, CS02/2A, CS06/6A, CS07/7A, CS11/11A, CS12/12A* and *CS14/14A*. However, the SPPS method could not produce enough product to meet the expected market requirement. Consequently, a Liquid Phase Peptide Synthesis (LPPS) method was introduced to facilitate manufacturing scale-up. The LPPS formulation was used in Phase II/III studies *CS18, CS15/15A* and *CS21/21A*. The LPPS formulation used in the pivotal Phase III study [CS21] is that proposed for registration.

The sponsor indicated that the physicochemical properties and specification limits of the SPPS and LPPS formulations have been compared in order to determine whether they were affected by the method of manufacture. These are matters for the quality evaluator. The sponsor also indicated that the effect of the physicochemical properties of degarelix on PKs was investigated in a rat model. These are matters for the nonclinical evaluator. In addition, the PK effects of the SPPS and LPPS formulations have been compared in a human PPK study using relevant data from the Phase I/II studies. The results from this study showed that median degarelix plasma concentrations were higher in the first month after administration of the LPPS formulation than the SPPS formulation.

Absorption

After SC degarelix administration a local *in situ* depot with a gel structure is formed. The gel appears to be formed as soon as degarelix comes into contact with tissue proteins. The release of degarelix from this *in situ* depot is bi-phasic in both healthy subjects and patients with prostate cancer. There is an initial rapid release phase occurring shortly after administration resulting in high plasma concentrations in the first few days after administration, followed by a prolonged slow release phase which determines the maintenance concentration. The data consistently showed that the SC PKs of degarelix in both healthy volunteers and patients were highly variable, and depended not only on the administered dose but the concentration of the injection solution. After the same SC dose, greater systemic exposure to degarelix occurred with low compared with high concentration injection solutions.

Single SC Starting Dose 240 mg

Data from the *pivotal study [CS21]* (ITT population) showed that respective mean and median C_{max} values were 61.2 ng/ml [range 0.530, 488] and 49.9 ng/mL in the pooled 240 mg group (n=409), and that t_{max} occurred in the first 24 hours after administration. The mean and median C_{min} (trough) values at Day 28 were 11.8 ng/mL [range 0.250, 49.2] and 11.1 ng/mL, respectively. In the *PPK [Phase 3] study*, median PK parameters were modelled using *pivotal study [CS21]* data after the 240 mg starting dose. The median simulated PK parameters with [5-95] percentile range after a single 240 mg dose were the area under the plasma concentration time curve from time zero to 28 days (AUC_{0-28d}) 1240 days.ng/mL [733-2140]; C_{max} 54.5 ng/mL [733-214]; C_{min} 10.7 ng/mL [6.3-18.7]; t_{max} 1.4 days [1.1-2.0]; and half-life ($t_{1/2}$) 42.5 days [26.96-72.6]. The population pharmacokinetic (PPK) data showed that median degarelix plasma concentrations were higher in the first month for the LPPS than for the SPPS formulation.

Maintenance SC Dose 80 mg

Data from the *pivotal study [CS21]* showed that steady state degarelix trough levels (C_{min}) were reached at days 308 and 336 for the 80 mg maintenance dose, with the respective mean and median values at Day 336 being 13.6 ng/mL [range 4.25, 207] and 10.9 ng/mL. In the *PPK [Phase 3] study*, simulated median steady state PK parameters with [5-95] percentiles for the 80 mg dose were the area under the plasma concentration-time curve from time 0 to Day 28 (AUC_{0-28d}) 664 days.ng/mL [425-1082]; C_{max} 70 ng/mL [42.2-115.4]; C_{min} 11.5 ng/mL [6.5-19.5]; and $t_{1/2}$ 27.7 days [17.79-46.9]. In an "end of Phase 2A" meeting between

the sponsor and the FDA the regulator expressed the view that target degarelix plasma trough concentration should be between 9-10 ng/mL rather than 7.37 ng/mL as proposed by the sponsor in order to have "fewer patients escaping [from serum testosterone suppression with concentrations ≤ 0.5 ng/mL] during maintenance dosing". The PPK observed and simulated median C_{min} values suggest that the majority of patients treated with the proposed 80 mg maintenance dose will achieve degarelix trough plasma concentrations > 9-10 ng/mL. However, there will be some patients treated with 80 mg whose trough concentrations will be < 9-10 ng/mL resulting in potentially inadequate serum testosterone suppression towards the end of the 28 day dosing interval. The observed and simulated median C_{min} values for the 160 mg maintenance dose were higher than the corresponding values for the 80 mg maintenance dose. This suggested that on PK grounds the higher maintenance dose might have been more clinically effective than the lower maintenance dose as fewer patients were likely to have escaped from testosterone suppression at the end of the 28 day dosing interval. However, in the pivotal clinical study [CS21] the 80 mg and 160 mg maintenance doses were of similar efficacy as regards the primary endpoint of testosterone suppression≤ 0.5 ng/mL from Day 28 to Day 364. This was predicted from the PPK study.

Absolute Bioavailability – Subcutaneous Administration

In healthy subjects, the absolute bioavailability of SC degarelix was estimated to be 32% based on dose-normalised AUC_t values and 39% based on dose-normalised area under the plasma concentration-time curve from time 0 to infinity (AUC_{inf}) values [CS05]. The IV AUC_{inf} was calculated using mean values across various IV dose levels rather than from a single dose. In addition, AUC values were derived from parallel group data with six subjects per group treated with either IV (4 groups) or SC (1 group) degarelix rather than from cross-over data in which patients were sequentially treated with IV and SC degarelix. The SC absolute bioavailability estimates from *study CS05* needs to be interpreted cautiously given the method used in its calculation.

Dose Proportionality

The data in patients with prostate cancer suggest that C_{max} and AUC increase with dose [CS07, C06]. However, the increases were not directly proportional to dose. Lack of direct dose proportionality might be due to high inter-subject variability.

Distribution

The steady state volume of distribution (V_{SS}) of degarelix in healthy elderly males (≥ 65 years) ranged from 0.65 to 0.82 L/kg and the volume of distribution in the terminal phase (V_z) ranged from 0.90 to 1.52 L/kg [CS08]. These data were based on IV degarelix infusions of 3.7 (n=6), 9.87 (n=6), 24.7 (n=9), and 49.4 (n=9) µg/kg. The high volume of distribution indicates that degarelix is widely distributed to the tissues. There were no data on volume of distribution after IV administration to patients with prostate cancer.

Plasma protein binding was determined in plasma samples collected at 1, 12, and 24 hours after the end of a 30 µg/kg IV infusion to 6 healthy males [CS05]. Mean protein binding was 90.7%, 90.5%, and 88.6% at 1, 12, and 24 hours post-infusion, respectively. In an *in vitro* study [1475/094], mean human plasma protein binding of degarelix was 90.5% over the concentration range 20 to 160 ng/mL. Binding to serum albumin (76.3%) and α1-acid glycoprotein (78.2%) was high in comparison with binding to high density lipoproteins (mean 57.9%) and gamma globulin (40.0%). There were no data on plasma-blood partitioning.

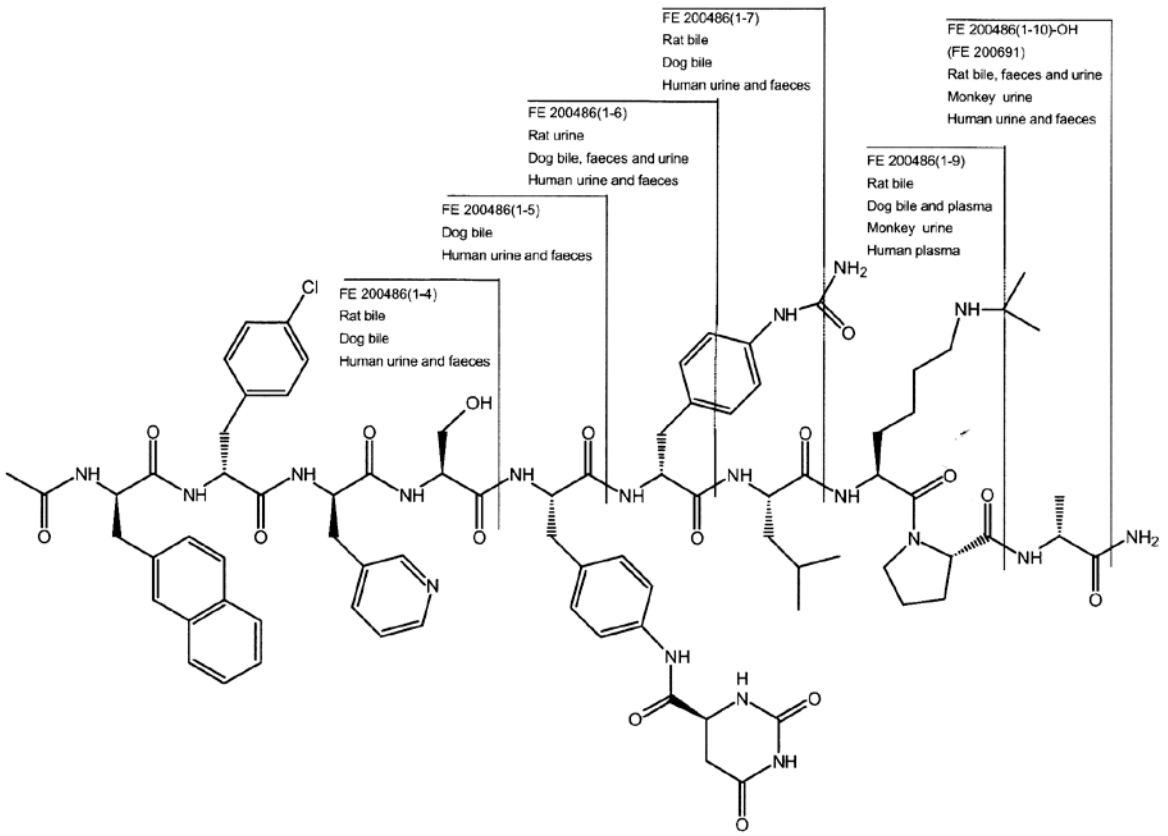
Metabolism

There were data on degarelix metabolites in human plasma, urine, and faeces from one study in healthy subjects [CS01], one study in subjects with hepatic impairment [CS23], and three studies in patients with prostate cancer [CS02, CS06, CS11]. The data showed that degarelix was eliminated predominantly unchanged in the urine, and as metabolic cleavage products in the faeces after hepato-biliary excretion. In both animals and humans, degarelix appears to undergo sequential proteolytic degradation (Figure 1). Apart from proteolytic cleavage products, no other metabolites (oxidation products or glucuronyl derivatives) were identified in the clinical studies. However, in an *in vitro* study in human microsomes, five oxidative metabolites of degarelix were identified accounting for < 1% in total of the administered dose. In another *in vitro study*, no degarelix derived peptides were found when degarelix at a concentration of 29 µM was incubated in human plasma over 60 minutes at 37°C. No glucuronic acid conjugates, mono-hydroxylated or truncated metabolites of degarelix were formed by *in vitro* metabolism in human liver microsomes. There were no mass balance studies on disposition in humans. Such studies would be difficult to undertake given the prolonged half-life of the drug. Furthermore, there would be ethical concerns relating to the use of radioactively labelled degarelix to determine disposition given the prolonged length of time subjects would be exposed to the label.

Metabolism Data from Clinical Studies

In [IAP-0176-00], 19 plasma samples from 4 healthy subjects from *study CS01* were analysed. Degarelix could be detected in all post-dose plasma samples analysed but no metabolites could be detected. In [REP-PD-0005.1], 249 plasma samples from 59 patients with prostate cancer from *study CS02* were analysed. Degarelix was identified in most analysed post-dose plasma samples, but no metabolites of degarelix were detected. In [REP-PD-0032.1], 42 urine samples were collected at 1 and 3 days after dosing from 21 patients with prostate cancer from *study CS06*. Degarelix was identified in all urine samples, but no metabolites were detected.

Figure 1: Degarelix cleavage products after proteolytic degradation.



In [DCB-A-0001], plasma (24 hours, 72 hours, and 7 days post-dose) and urine samples (24 hours and 72 hours post-dose) from 18 Japanese patients with prostate cancer from *study CS11* were analysed. Degarelix was detected in all post-dose plasma samples and in most samples accounted for 90-100% of the compound-related material detected. One metabolite, FE 200486 (1-9), was detected in 19 of the 54 post-dose plasma samples. Unchanged degarelix was detected in all post-dose urine samples and accounted for more than 84% of the total amount of compound-related material detected in the urine. Three metabolites, FE 200486 (1-4), FE 200486 (1-5) and FE 200486 (1-6) were detected in most post-dose urine samples. Two metabolites, FE 200486 (1-10)-OH and FE 200486 (1-7), were detected in a few post-dose urine samples. The five metabolites identified in the post-dose urine samples accounted for 2-16% of the compound-related material detected. No other metabolites were detected in the plasma and urine other than those mentioned. The detection of metabolites in human plasma and urine in subjects from *study CS11* is in contrast to studies in subjects from *studies CS01, CS02* and *CS06* which failed to detect metabolites in the plasma and/or urine. The investigators attributed the differences to the more sensitive analytical method used in [CS11] rather than differences between Japanese and Caucasian subjects, and/or differences between healthy subjects and patients with prostate cancer.

In [DCB-A-0019], plasma, urine and faeces samples from healthy and hepatically impaired subjects from *study CS23* were analysed. The plasma samples were collected pre-dose and then post-dose at 4, 12, and 72 hours. In plasma, degarelix was detected in 81 of 96 post-dose

samples, and accounted for 90-100% of the compound-related material detected. One metabolite, FE 200486 (1-9), was detected in amounts of up to about 10% in most of the 4 and 12 hour post-dose plasma samples. *In urine*, degarelix was detected in nearly all samples and in most of these samples it accounted for more than 85-95% of the total amount of compound-related material detected. Three main metabolites, FE 200486 (1-4), FE 200486 (1-5) and FE 200486 (1-6) were detected in most post-dose urine samples. Two metabolites were detected only in hepatically impaired subjects with one, FE 200486 (1-7), being detected in 7 samples and one, FE 200486 (1-10)-OH, detected in 1 sample. In the urine, metabolites accounted for 2-15% of the total amount of compound-related material detected. In *the faeces*, degarelix in amounts below 15% was detected in 9 of the 62 post-dose samples. FE 200486 (1-5) was the most prominent metabolite and was detected in 56 of the 62 post-dose faeces samples, and in 38 of these it was the major metabolite present. FE 200486 (1-4) was the second most prominent metabolite detected in the faeces being found in 50 of the 62 post-dose samples. In 18 post-dose faeces samples, FE 200486 (1-4) was the major metabolite detected and 16 of these 18 samples were from hepatically impaired subjects. Other metabolites detected in the faeces were FE 200486 (1-6), FE 200486 (1-7), FE 200486 (1-9) and FE 200486 (1-10)-OH. The metabolite profiles of healthy and hepatically impaired subjects were similar.

Metabolism Data from Human Liver Microsomes

In [IAP-0193-00], *in vitro* metabolism of degarelix at a concentration of 40.4 μM by CYP450 isoenzymes was investigated in human liver microsomes. The test concentration was approximately three orders of magnitude higher than the plasma concentration of degarelix obtained 12 hours after a SC injection of 40 mg in healthy males. Six metabolites were detected and five of these were oxidative metabolites of degarelix. The total amount of oxidative metabolites detected was low (< 1% of the initial amount of degarelix) indicating that degarelix is likely to be a poor substrate for human CYP450 isoenzymes. The sixth metabolite (~ 2% of the initial amount of degarelix) was probably formed by proteases and not by CYP450 isoenzymes.

Excretion

In healthy men, approximately 20-30% of an administered IV dose of degarelix was excreted unchanged in the urine [CS05, CS23]. These data and the *in vitro* metabolite data suggest that 70-80% of an administered dose is excreted as degarelix cleavage products via the hepato-biliary system. The mean (standard deviation [SD]) fraction of degarelix excreted unchanged in the urine after 48 hours was 18.5% (5.1%) after IV administration of four dose levels in healthy male subjects (n=24) [CS05]. The four IV doses were 1.5, 6.0, 15, and 30 μg/mL with 6 subjects per dose. The fraction of degarelix excreted unchanged after 72 hours was approximately 31% after IV administration of 1 mg to a smaller number of healthy male subjects (n=8) [CS23]. In this study, the majority of the remainder of the administered dose appeared to be eliminated by the hepato-biliary system as degarelix cleavage products. The difference in the fraction excreted unchanged in the urine between the two studies of about 10% is probably a reflection of inter-subject variability.

The mean (SD) total and renal clearance were 3.73 (1.06) and 0.67 (0.26) L/hr, respectively, in healthy male subjects (n=24) after escalating dose IV infusion [CS05]. The mean (SD) clearance after escalating dose IV infusions was in the range 35(7) to 47(12) mL/h/kg in healthy elderly males (≥ 65 years) [CS08]. The [CS08] data were based on IV degarelix infusions of 3.7 (n=6), 9.87 (n=6), 24.7 (n=9), and 49.4 (n=9) μg/kg. In the *PPK [Phase 3] study*, it was estimated that clearance (CL) [SE] was 3.16 [0.17] L/h in patients with normal renal function (creatinine clearance [CLcr] > 80 mL/min) and decreased with increasing age

at a rate of 0.6% per year. The CL estimate of 3.16 L/h equates to about 40.5 mL/h/kg based on a weight of 78 kg used for the calculation of CL in the PPK [Phase 3] study.

The mean (SD) half-life of degarelix after IV infusion was in the range 13.6 (2.5) to 23.7 (2.8) hours in healthy elderly males (≥ 65 years) [CS08]. The mean half-life after a single SC 80 mg dose (20 mg/mL solution) was about 41 days [range 28-61] in patients with prostate cancer, and after a single SC 160 mg dose (40 mg/mL solution) was about 25 days [range 12-69] [CS06]. The median [range] half-life of degarelix after a single SC dose of 240 mg (40 mg/mL solution) was about 53 days [range 29-104] in patients with prostate cancer [CS07]. These data show that the half-life after SC administration is markedly longer than that after IV administration. Consequently, the rate of elimination of degarelix is determined by its rate of absorption from the SC depot (ie the rate of absorption is the rate limiting step in elimination).

Pharmacokinetics in Special Groups

Hepatic Impairment

There was one Phase I study in subjects with hepatic impairment [CS23]. The study included 24 male subjects of mean age 49 years [range 34-68 years]. It was conducted in three parallel groups of 8 subjects each: mild hepatic impairment (Child-Pugh score ≤ 6; Grade A); moderate hepatic impairment (Child-Pugh score 7-9; Grade B);[4] and healthy subjects with normal hepatic function matched to patients with impaired hepatic function with regards to age (±10 years) and body weight (±10%). The hepato-biliary disorders described in the 16 subjects with hepatic impairment were: 10 with alcoholic cirrhosis, 6 with hepatic cirrhosis, 3 with portal hypertensive gastropathy, 1 with autoimmune hepatitis, and 1 with cholelithiasis. Subjects could have more than one hepato-biliary disorder. Hepatitis C was present in 3 subjects and hepatitis B in 2 subjects. Each subject was given a single 1 mg dose of degarelix administered as an IV infusion over 1 hour. The dose was expected to give a median C_{max} of 54 ng/mL, a value similar to that observed after a single SC dose of 240 mg (40 mg/mL) [CS21]. Blood was collected pre-dose and then at intervals from 10 minutes to 72 hours post-dose.

The primary endpoints were AUC_{inf}, AUC_t, and C_{max}. Hepatic impairment was considered to have no effect if the 90% CIs for the ratios of the geometric means of the primary PK endpoints for hepatic impairment and control groups were all in the range 0.8-1.25. The results showed that both mild and moderate hepatic impairment groups had lower AUC_{inf}, AUC_t, and C_{max} mean values than the healthy group. None of the 90% CIs for the relevant ratios were completely within the range 0.8-1.25. Exploratory comparisons showed that subjects with mild and moderate hepatic impairment had higher CL and Vz mean values and longer $t_{1/2}$ mean values than healthy subjects. The fraction of the administered dose cleared unchanged by the kidneys was about 30% in both hepatically impaired and healthy subjects. Plasma protein binding at 1 hour after the end of the infusion was unchanged by hepatic impairment and was about 90% in all groups

Comment

The data from *study CS23* showed that lower C_{max}, AUC_{inf}, and AUC_t mean values were observed in hepatically impaired subjects compared with healthy subjects. This appears to be

[4] The **Child-Pugh score** is used to assess the prognosis of chronic liver disease. The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

due to increased CL in hepatically impaired subjects, but the reason for the difference in CL between hepatically impaired and healthy subjects is unknown. The data suggest that hepatic metabolism of degarelix is not significantly affected by hepatic impairment. In the *PPK [Phase 3] study*, the model showed trough degarelix values to be virtually indistinguishable between healthy and hepatically impaired subjects, while peak values were less than 10 % lower for moderately impaired subjects compared to healthy subjects. The data from *study CS23* and PPK modelling suggest that degarelix dose modification is unlikely to be required in patients with mild or moderate hepatic impairment. There are no data on patients with severe hepatic impairment.

Other Special Groups

There were no studies in subjects with *renal impairment*. The PK data showed that about 20-30% of an administered dose was eliminated unchanged in the urine [CS05, CS23], while renal clearance was 0.67 (0.26) L/hr in healthy males [CS05]. Data from the *PPK [Phase 3] study*, estimated CL to be 3.16 L/h in patients with prostate cancer with normal renal function (creatinine clearance [CLcr] > 80 mL/min), while in patients with moderate renal impairment (CLcr 30-50 mL/min) CL was on average reduced by 23%. Overall, the available PK data suggest that dosage adjustment is not required in patients with moderate renal impairment, but there are no data on patients with severe renal impairment. Data from the *PPK [Phase 3] study* estimates that CL decreases with increasing age at the rate of 0.6% per year. The PK data showed no significant differences between *Caucasian and Japanese* subjects. PK data in *females, children, and adolescents* are considered to be unnecessary for the proposed indication.

Pharmacokinetic Studies in Healthy Subjects

Study CS05 – Bioavailability Study

The sponsor identified *study CS05* as the relevant bioavailability study. It was an open-label, single-dose study in 36 healthy Caucasian males with an average age of 33.2 years. The study investigated the safety, PKs, and PD of single doses of degarelix given as IV infusions, SC injections or IM injections. It included 6 treatment groups (4 x IV, 1 x SC, 1 x IM) with 6 subjects in each group. The description of results centres on the SC group (n=6) in which subjects were given a single 20 mg (5 mg/mL) dose as two simultaneous SC injections (2 x 2 mL). Median degarelix plasma concentrations increased rapidly and steeply after SC administration and then declined to remain stable from 7 to 28 days. The PK results for the SC dose are summarised below in Table 7.

Table 7: Pharmacokinetic parameters of degarelix 20 mg after SC administration (n=6) [CS05].

	AUCinf (h.ng/mL)	AUCt (h.ng/mL)	AUCextrap (%)	Cmax (ng/mL)	Tmax h	t1/2 h
Mean (SD)	2360 (690)	1754 (629)	27 (7)	6.7 (1.8)	12 (13)	557 (107)
Median	2296	1565	27	6.5	5	525
Range	1396-3133	971-2543	19-35	4.4-9.0	3-36	467-758

.

The mean (SD) fraction of degarelix excreted unchanged was 18.5% (5.1%) [range 19.6, 25.3] after administration of the four IV doses to 24 subjects. The mean (SD) total clearance was 3.37 (1.06) L/h [range 2.18, 6.45] and the mean (SD) renal clearance was 0.67 (0.26) [range 0.28, 1.17] after IV administration (n=24). The SC absolute bioavailability was estimated to be 32% based on the dose-normalised AUC_t and 39% based on the dose-

normalised AUC_{inf}. The mean terminal half-life after SC administration (557 hours) was markedly longer than that after IV administration (3-16 hours).

Study CS01

In *study CS01*, dose related PK of degarelix after single SC doses were assessed. Both the C_{max} and AUC_t increased with dose. The highest geometric mean C_{max} and AUC_t values were observed with the 40 mg dose (10 mg/mL), and the median half-life at this dose was 41 days [range 31-49]. Slow elimination of degarelix meant that a large proportion of the AUC_{inf} values were extrapolated. In the *fixed degarelix dose* regimens, higher systemic exposure occurred with lower concentration injection solutions and higher injection volumes.

Pharmacokinetic Studies in Patients with Prostate Cancer

Study CS06

In *study CS06*, the PK of degarelix after single SC injections ranging from 40 mg to 160 mg were investigated in patients with prostate cancer. The four doses and concentrations of degarelix investigated in this study were 40 mg (10 mg/mL), 80 mg (20 mg/mL), 120 mg (30 mg/mL) and 160 mg (40 mg/mL), with the volume of each dose being 4 mL (2 x 2 mL injections). The geometric mean and median values for C_{max} and AUC_{inf} increased with dose over the range 40 mg to 160 mg, while the geometric mean and median values for AUC_t increased with dose over the range 40 mg to 120 mg. However, increases in these parameters were not directly proportional to dose. The PK after single SC 80 mg (20 mg/mL) and 160 mg (40 mg/mL) doses are summarised below in Table 8. The results show that although the dose was doubled, the AUC_t only increased by a factor of 1.04 and the C_{max} by a factor of 1.3. The concentration of the 80 mg dose injection solution was lower than that of the 160 mg dose injection solution (20 mg/mL vs 40 mg/mL), and as shown in a number of studies lower concentration injection solutions result in higher systemic exposure than lower strength injection solutions. The results also showed high inter-subject variability in the PK parameters.

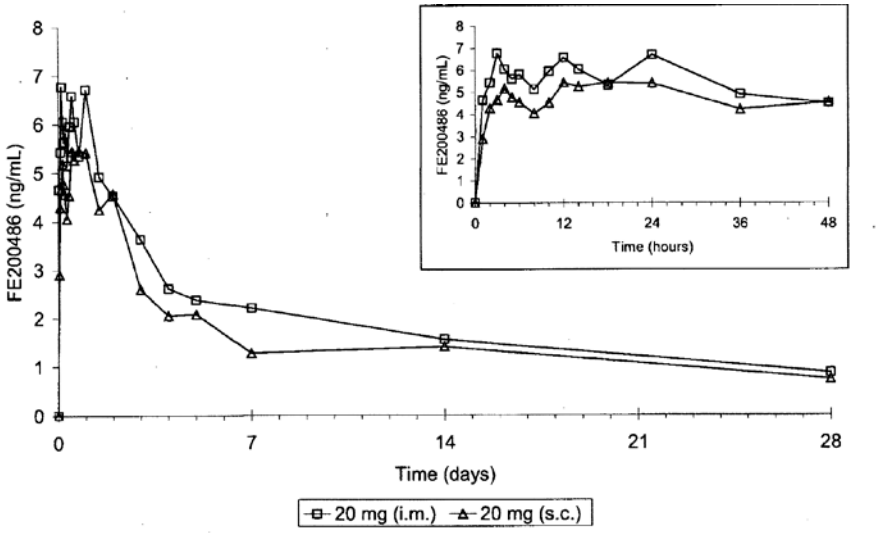
Table 8: PK parameters after degarelix 80 mg and 160 mg SC in patients with prostate cancer [CS06].

		AUC_{inf} day.ng/mL [2]	AUC_t day.ng/mL [2]	C_{max} ng/mL [2]	T_{max} hr [3]	$T_{1/2}$ day [4]
80 mg	n	19	24	24	24	19
20 mg/mL	GM (CV%) [1]	479.06 (33.72)	292.97 (68.83)	14.48 (21.90)	43.69 (23.3)	40.96
4 mL inj	Median	471	350	14.65	26.3	42.0
	Min-Max	275-842	98-759	9.60-24.78	22.25-76.02	28.12-60.77
160 mg	n	8	21	21	21	8
40 mg/mL	GM (CV%) [1]	782.55 (38.39)	306.51 (93.07)	18.53 (92.17)	55.10 (23.60)	25.44
4 mL inj	Median	781	283	16.42	71.33	33.68
	Min-Max	443-1599	81-1497	7.74-152.22	23.33-78.52	11.81-69.12

1 = Geometric Mean (Coefficient of variation %). 2 = GM (CV%). 3 = Arithmetic Mean (Standard Deviation). 4 = Harmonic Mean.

The median degarelix plasma concentration profiles after 20 mg IM and SC are summarised below in Figure 2. Concentrations rapidly increased after SC administration peaking at about 4-6 hours and remaining at these levels for about 2-3 days, after which they rapidly declined to reach a level at 7 days which stayed relatively stable to the end of 28 day observation period.

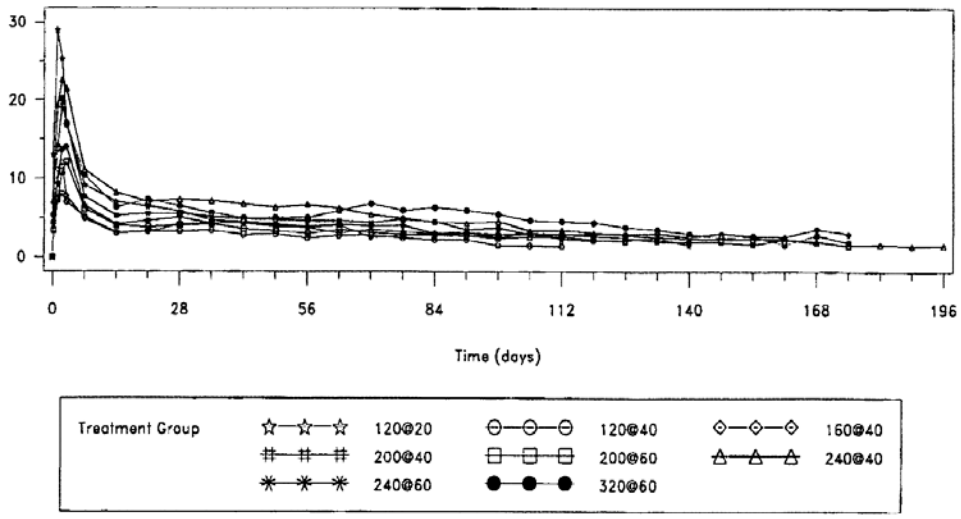
Figure 2: Median degarelix plasma concentration time profiles after IM and SC administration [CS05].


FE200486 (ng/mL)
Time (days)
20 mg (i.m.)
20 mg (s.c.)
FE200486 (ng/mL)
Time (hours)

Study CS07

In *study CS07*, the PK of degarelix were investigated after single SC injections ranging from 120 mg to 320 mg in patients with prostate cancer. The study included 8 single dose SC degarelix treatment groups of 120 mg (20 mg/mL); 120 mg (40 mg/mL); 160 mg/mL (40 mg/mL); 200 mg (40 mg/mL); 200 mg (40 mg/mL); 240 mg (40 mg/mL); 240 mg (60 mg/mL) and 320 mg (60 mg/mL). The geometric median degarelix plasma concentration curves are provided below in Figure 3.

Figure 3: Median degarelix plasma concentrations [CS07].



Degarelix plasma concentrations rapidly increased after administration in all treatment groups with the mean t_{max} ranging from 1.4 days for 120 mg (20 mg/mL) to 2.5 days for 200 mg (60 mg/mL). Systemic exposure was inversely related to the concentration of the injection solution. An example of this can be seen for a 240 mg dose administered in concentrations of 40 mg/mL or 60 mg/mL where the respective geometric mean $AUC_{0\text{-}3days}$ values were 59.3 and 25.5 day.ng/mL, and the respective C_{max} values were 26.2 and 11.8 ng/mL. If the concentration of the injection solution was kept constant then systemic exposure to degarelix increased with dose, although the increases were not directly proportional. An example of this can be seen below in Table 9, where C_{max}, $AUC_{0\text{-}3days}$, AUC_t, and AUC_{inf} increased with dose when the injection solution concentration was kept constant. High inter-subject variability was seen for the PK parameters for all doses.

The harmonic mean half-life for the 40 mg/mL solution groups varied from 72.9 days for the 120 mg dose (n=7) to 53.3 days for the 240 mg dose (n=21). The value for the higher dose might be more reliable than that for the lower dose group as it is based on a larger number of patients. The half-life (and consequently the AUC_{inf}) could not be estimated for all treatment groups (particularly those in which the 60 mg/mL concentration was used) due the study ending before degarelix had been completely eliminated.

Table 9: Pharmacokinetic parameters after SC degarelix 120, 160, 200, and 240 mg administered as a 40 mg/mL injection solution in patients with prostate cancer [CS07].

		AUC_{0-3d} day.ng/mL	AUC_t day.ng/mL	AUC_{inf} day.ng/mL	C_{max} ng/mL
120 mg	n	12	12	7	12
40 mg/mL	GM (CV%) [1]	21.4 (27.2)	190 (92.9)	520 (14.7)	9.04 (27.6)
160 mg	n	12	12	5	12
40 mg/mL	GM (CV%) [1]	27.7 (42.6)	182 (114)	641 (28.8)	11.8 (43.9)
200 mg	n	24	24	19	24
40 mg/mL	GM (CV%) [1]	42.4 (33.3)	593 (40.5)	829 (29.8)	18.7 (38.1)
240 mg	n	24	24	21	24
40 mg/mL	GM (CV%) [1]	59.3 (77.8)	750 (64.3)	1054 (34.8)	26.2 (83.4)

1 Geometric Mean (Coefficient of variation %).

Study CS21

In the pivotal study [CS21], following the 240 mg starting dose the mean degarelix plasma concentrations peaked (C_{max}) on Day 1 with the respective values for the 240/160 mg (n=198) and 240/80 mg (n=206) regimens being 61.5 ng/mL [range 0.53, 372] and 61.0 ng/mL [range 14.9, 488]. At Day 28 the respective mean levels (trough concentrations) had fallen to 11.9 ng/mL [range 2.80, 41.7] (n=192) and 11.8 [ng/mL] (n=203). Steady state trough concentrations were reached on days 308 and 336 with the respective levels being 22.1 ng/mL [range 5.01, 123] (n=167) and 20.2 ng/mL [range 4.35, 170] (n=165) for the 160 mg maintenance regimen, and 13.5 ng/mL [range 4.99, 163] (n=170) and 13.6 ng/mL [range 4.25, 207] (n=169) for the 80 mg maintenance regimen. Marked inter-subject variability was observed in the plasma concentrations.

High Trough Degarelix Plasma Concentration in a Subset of Patients

Persistently high trough plasma degarelix concentrations (above 100 ng/mL in at least two PK trough samples) were observed in 9 patients from the Phase II [CS12/CS12A, S14/CS14A, CS15/CS15A], and Phase III [CS21/CS21A] studies. On the basis of CLcr, 4 of 9 patients were classified as having mild renal impairment and 2 of 9 as having moderate renal impairment. Persistent testosterone escape was observed in 2 of 9 patients. The adverse drug reaction (ADR) pattern in the 9 patients did not differ from that of all treated patients. Potential explanatory mechanisms for the persistently high trough plasma concentrations were considered to include: changes in the depot formation; impaired metabolism (genetically based or due to hepatic dysfunction); reduced renal excretion; change in protein binding; antibody formation. Of these potential mechanisms, anti-degarelix anti-bodies were detected in all 9 patients, and the sponsor noted that decreased renal clearance as a result of antibody formation has been described for lepirudin (a thrombin inhibiting peptide used for the treatment of thrombocytopenia). In 7 of 9 subjects, it was estimated that the CL was less than 1.83 L/h. It was postulated that a combination of factors such as renal impairment resulting in low CL, anti-degarelix antibody formation, and increased bioavailability might have contributed to high trough plasma concentrations in this small number of patients. The significance of this observation in 9 subjects should be interpreted in the context of more than 20,000 PK samples from 1297 patients from the Phase II and III studies. It is considered that the observed high trough levels are unlikely to be clinically significant as regards the proposed treatment regimen.

Population Pharmacokinetic (PPK) Modelling (Phase 2/3 Studies)

The PPK model (Nonmem version VI) included two disposition compartments and two dosing compartments corresponding to the fast and slow release phases of degarelix from the SC depot to describe the degarelix concentration data. The model included IV data from 24 healthy males [CS05], and SC data from 857 patients with prostate cancer [CS06/6A, CS07/7A, CS12/12A, CS14/14A, CS15]. The mean age, weight, and body mass index (BMI) of the healthy volunteers were about 34 years, 81 kg, and 25.0 kg/m^2 and the respective corresponding values for the patients with prostate cancer ranged from 71-76 years, 78-82 kg and 26.0-27 kg/m^2. The model included data from the two formulations used in the Phase I/II studies (SPPS and LPPS).

Median degarelix plasma concentration-time profiles were constructed after single SC dosing of 80 mg (20 mg/mL SPPS) [CS06], 160 mg/mL (40 mg/mL SPPS) [CS07], 240 mg (40 mg/mL SPPS) [CS07], 240 mg (60 mg/mL SPPS) [CS07], and 240 mg/mL (40 mg/mL LPPS) [CS15]. The concentration-time profiles showed that median systemic exposure to degarelix (relative to dose) decreased with increasing injection solution concentration. The concentration-time profiles showed that for the 240 mg (40 mg/mL) dose the LPPS formulation resulted in higher median degarelix plasma concentrations than the SPPS formulation in the first month after administration. The CL (SE) was estimated to be 2.19 (0.13) L/h and decreased with increasing age at the rate of 1% per year.

Population Pharmacokinetic Modelling (Phase 3).

The PPK model (Nonmen version VI) used in this study was similar to that used in the *PPK [2/3] study*. The model included SC degarelix PK data from *the pivotal study [CS21]* from 409 patients with prostate cancer treated with a starting dose of 240 mg (40 mg/mL LPPS) followed by maintenance treatment with either 160 mg (40 mg/mL LPPS) or 80 mg (20 mg/mL LPPS) every 28 days for 1 year. The model also included IV degarelix PK data from *study CS08* from 42 healthy elderly males (aged≥ 65 years) treated with one of six degarelix IV infusion regimens adjusted over time to keep the concentration constant. The two lowest dose groups in study CS08 were excluded since these did not reach clinically relevant degarelix concentration levels. Degarelix concentrations below the LLOQ (0.5 ng/mL) were also excluded (5 from study CS21; 50 from study CS08). The populations from study CS08 and study CS21 were similar with respect to median age (67.7 and 71.8 years, respectively) and weight (78.1 and 79.2 kg, respectively) but creatinine clearance was 20% higher in study CS08 than study CS21 (86.0 vs 70.4 mL/min). The results for the SC PK parameters after a single 240 mg (40 mg/mL) dose of degarelix and maintenance doses of 80 mg (20 mg/mL) and 160 mg (40 mg/mL) are summarised below in Table 10.

Table 10: Simulated and observed median (5-95 percentiles) in PK parameters PPK [Phase 3] study.

Median (5-95 percentiles) Values	**80 mg (20 mg/mL) Steady State**	**160 mg/mL (40 mg/mL) Steady State**	**240 mg (40 mg/mL) Single Dose**
Simulated AUC days. ng/mL	664 (425-1082)	820 (488-1400)	1240 (733-2140)
Simulated C_{max} ng/mL	70.0 (42.2-115.4)	57.0 (32.6-101.4)	54.5 (28.8-110.4)
Observed C_{max} ng/mL	-	-	53.4 (27.3-126.5)
Simulated C_{min} ng/mL*	11.5 (6.5-19.5)	19.9 (11.4-34.1)	10.7 (6.3-18.7)
Observed C_{min} ng/mL *	10.9 (5.7-22.2)	20.2 (8.9-43.3)	11.1 (6.2-20.2)
Simulated t_{max} days	-	-	1.4 (1.1-2.0)
Simulated $t_{½}$ days	27.7 (17.7-46.9)	-	42.5 (26.9-72.6)

*Day 28 value for single dose.

The concentration of the injection solution had statistically significant effects ($p<0.001$) on absorption parameters with 20 mg/mL resulting in a higher fast absorbed dose fraction (32.0% vs 14.9%), a higher bioavailability (58.4% vs 35.6%) but a shorter terminal half-life (635 h vs 991 h) than 40 mg/mL. The CL [SE] was 3.16 [0.17] L/h in patients with normal renal function (CLcr > 80 mL/min). Patients with moderate renal impairment (CLcr 30-50 mL/min) had, on average, a 23% reduced clearance compared with subjects with normal renal function. The CL [SE] L/h decreased with increasing age at a rate of 0.6% per year, and increased with weight at a rate of 0.7% per kg.

Drug Interactions

There were no *in vivo* drug-drug PK interaction studies in humans. However, there were no signals from four *in vitro* interaction studies suggesting that degarelix is likely to significantly interact with other drugs. The data from these four *in vitro* studies, together with that from the human metabolite studies, indicate that clinically significant interactions between degarelix and other drugs are unlikely. Consequently, the lack of clinical drug-drug interaction is considered to be acceptable. The four *in vitro* studies are reviewed below

No inhibitory effects of degarelix were observed on CYP450 isoenzymes (CYPlA2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5) in human liver microsomes at concentrations approximating up to 100 times the expected human plasma concentration of a pharmacologically active dose [IAP-0146-01]. No inhibitory effect of degarelix on CYP2C9 activity was found at concentrations 1-10,000 nM [AR-DCB-0008.01]. However, degarelix slightly increased CYP2C9 activity although the effect did not appear to be dose dependent. The increased CYP2C9 activity is unlikely to indicate enzyme induction as the human liver microsome system lacked the pre-requisites for protein synthesis. Degarelix did not induce activity of CYPlA2, CYP3A4 and CYP2C9 in cryopreserved plateable human hepatocytes at concentrations 0.1, 1, and 10 μM [AR-DCB-0025.1].

The effects of degarelix on four human drug efflux transporters (PgP/MDR1 [ABCB1], BCRP/MXR [ABCG2], MRP2 [ADCC2], BSEP [ABCB11/sPsP]) and three human uptake transporters (OATP1B1, OATP1B3, OATP2B1) were investigated in *Study [FE200486-2280]*. A number of assays specific for the mechanism being studied were used (that is, ATPase assays, indirect vesicular transport assays, fluorescent dye efflux assays, and cell based uptake transporter assays). At concentrations above 10 μM degarelix showed several interactions with different components of the assays preventing potential interactions being detected. However, at concentrations up to 10 μM degarelix did not show any interaction with PgP, BCRP, MRP2, BSEP, OATP1Bl and OATP2B1. Degarelix inhibited OATP1B3 mediated fluo-3 transport with an IC_{50} of 10 μM, but the concentration range of this interaction was very close to the concentrations where non-specific inhibitory effects were observed for all assays. Consequently, it is not clear whether the observed interaction was specific for OATP1B3. Overall, the data suggest that interactions between degarelix and drugs handled by efflux and/or uptake transporters are unlikely to be significant at expected degarelix plasma concentrations.

Efficacy

The submission included one pivotal, Phase III, open-labelled, active-controlled, efficacy study [CS21], and four, Phase II, open-labelled, uncontrolled, supportive efficacy studies [CS07, CS12, CS15, CS15]. The supportive efficacy studies included information on starting and/or maintenance doses directly relevant to the treatment regimen being proposed for registration. There were no adequate efficacy data beyond 12 months of treatment. The effect of degarelix on testosterone suppression was the primary efficacy objective of the pivotal and supportive clinical studies. The initial protocols of most of the efficacy studies underwent

modification and amendment following specific regulatory advice from the FDA to the sponsor on such matters as endpoint definition and statistical analysis of the endpoints.

Supportive Studies

Supportive Studies - Maintenance Dose - Studies CS12 and CS14

The *protocol specified primary objective* in both [CS12] and [CS14] was to demonstrate the efficacy of different degarelix dosing regimens by comparing testosterone suppression (serum testosterone ≤ 0.5 ng/mL) after 196 days (7 cycles) of treatment. However, subsequent analysis centred on the 28 to 364 Day rather than the 28 to 196 Day data for 12 rather than 7 treatment cycles. *Design* in both studies was multi-centred, open-label, randomised, uncontrolled and parallel-group.

In *study CS12*, six SC degarelix *treatment regimens* were investigated with a starting dose of 200 mg or 240 mg followed by a maintenance dose of 80 mg (40 mg/mL), 120 mg (40 mg/mL) or 160 mg (40 mg/mL) every 28 days for a maximum of 12 cycles. In *study CS14*, two SC degarelix *treatment regimens* were investigated, both with a starting dose of 200 mg (40 mg/ml) followed by a maintenance dose of 60 mg (20 mg/mL) or 80 mg (20 mg/mL) every 28 days for 12 cycles.

The *inclusion criteria* were similar for both studies and included patients aged at least 18 years with histologically confirmed adenocarcinoma of the prostate (all stages) in whom hormonal treatment was indicated (except for hormonal neoadjuvant treatment). Patients were also required to have a life expectancy of at least 6 months and an ECOG (Eastern Co-operative Oncology Group) score of ≤ 2. In addition, baseline serum testosterone concentration had to be above the lower limit of the normal range and the PSA had to be≥ 2 ng/mL. The *exclusion criteria* were similar for both studies and included patients with previous or current hormonal management of prostate cancer. However, previous neoadjuvant hormonal therapy was acceptable in patients having undergone prostatectomy or radiotherapy with curative intention provided it had been given for no more than 6 months and had ceased at least 6 months prior to screening. In addition, patients were excluded if considered to be candidates for curative therapy within 6 months of screening.

Patients

In *study CS12*, 216 patients were screened, 189 were randomised to treatment and 187 were exposed to degarelix. Of the 189 randomised patients, 147 (77.8%) completed the study and 42 (22.2%) withdrew. The reasons for the 42 withdrawals were: 16 due to inadequate testosterone suppression; 13 due to adverse events (AEs); and 13 for other reasons (7 consent withdrawn, 2 non-compliance with protocol, 2 lost to follow-up, 1 PSA progression, 1 exclusion criteria violated). The mean age of the 187 patients exposed to degarelix was 71 years [range 52-93], mean weight was 79 kg [range 50-150], mean height was 1.73 m [range 1.58-1.94], and mean BMI was 26 kg/m^2 [range 18-41]. The ethnic background was 96% white, 3% black of African heritage, and <1% Asian. The demographic characteristics were similar for the six treatment groups.

In *study CS14*, 176 patients were screened, 127 were randomised and all were exposed to degarelix. Of the 127 randomised patients, 87 (68.5%) completed the study and 40 (31.5%) withdrew. The reasons for the 40 withdrawals were: 16 due to inadequate testosterone suppression; 6 due to AEs; 5 for protocol violations; 5 withdrawals of consent; 4 withdrawn by the investigator; and 4 for other reasons. The mean age of the 127 patients exposed to degarelix was 74.8 years [range 28-87], mean weight 83 kg [range 51-135], mean height 1.74 m [range 1.5-1.91], and mean BMI 27.3 kg/m^2 [range 19.1-39.2]. The ethnic background was 76% white, 22% black of African heritage, and 2% Asian. The demographics of the two

treatment groups were similar except for a higher proportion of blacks of African heritage in the 200/60 group (22%) compared with the 200/80 group (6%).

Primary and Secondary Efficacy Endpoints

A *co-primary primary efficacy endpoint* for both studies was the proportion of patients with serum testosterone level ≤ 0.5 ng/mL from Day 28 to Day 196, and from Day 28 to Day 364. The initial focus in the protocol was on the Day 28 to 196 data. However, the Day 28 to 364 data appeared to assume greater importance than the Day 28 to Day 196 data after regulatory advice from the FDA.

The other *co-primary efficacy endpoint* for both studies was the proportion of patients with testosterone level ≤ 0.5 ng/mL from Day 28 to Day 196, and from Day 28 to Day 364, in patients with testosterone ≤ 0.5 ng/mL at Day 28. These endpoints were included in the study following regulatory advice from the FDA. They assess "pure" maintenance response as they measure the ability of treatment to maintain serum testosterone concentrations of ≤ 0.5 ng/mL at Day 28 through to Day 196 (or Day 364).

The *results* for the two studies are presented separately and centre on the Day 28 to Day 364 primary efficacy endpoint data rather than the Day 28 to 196 data. It is considered that the longer maintenance treatment period is more clinically relevant as it is likely that degarelix will be used for long-term treatment. Both studies included a number of *similar secondary efficacy endpoints* assessing various testosterone, DHT, PSA, LH, FSH, and SHBG parameters and the results for selected endpoints have also been briefly reviewed.

Statistical Method and Sample Size

In both studies, the primary analysis was in the intent-to treat (ITT) completers analysis set, with analysis also being undertaken in the ITT and the per protocol (PP) analysis sets. The *ITT analysis* set included all randomised patients who received at least one dose of degarelix. The *ITT completers analysis set* on Day 196 (or Day 364) included all patients in the ITT analysis who either attended the Day 196 (or Day 364) visit or had a testosterone measurement > 0.5 ng/mL on Day 28 and onwards. All patients with testosterone levels≤ 0.5 ng/mL on Day 28 and onwards, but withdrawn before Day 196 (or Day 364), were excluded from the ITT completers analysis set. The rationale for the *ITT completers analysis set* was that it is conservative in estimating testosterone response rates at Day 196 (or Day 364) because early withdrawals (even though suppressed) are not carried forward. The *ITT completers analysis set* was added after FDA regulatory advice.

In both studies, the primary endpoints were analysed using general linear models based on the binomial distribution. All statistical tests were two-sided and all confidence intervals were 95%. However, no adjustments for multiple testing were made. Power calculations were provided in the *Protocols and Statistical Analysis Plans* for both studies based on the number of randomised patients in each treatment group and on a two-sided continuity corrected chi-square test and 5% significance level. Based on these assumptions both studies had a power of approximately 80% to detect a difference in response between two maintenance doses of 95% versus 75%. However, the power calculations are of uncertain relevance as the studies assessed the difference between proportions using generalised linear models based on the binomial distribution rather than the statistical methods described in the protocols. In the *ITT completers analysis set*, comparisons between doses were also made by estimating the absolute difference in the primary efficacy endpoint response rates by exact methods for 2 x 2 contingency tables.

Study CS12 – Efficacy Results

In this study, factors included in the generalised linear model (GLM) were the initial and maintenance dose, and the interaction between these two factors. The test of main effects (initial and maintenance doses) was performed in a model without the interaction term. Doses in the model were log transformed and divided by the difference between maximum and minimum dose on the log scale. This rescaling was done in order to have the odds ratios compare odds between the minimum and maximum initial or maintenance dose.

Co-Primary Efficacy Endpoint – Suppression from 28 to 364 days

The results showed that the proportion of patients suppressed (serum testosterone concentration ≤ 0.5 ng/mL) in the period from 28 to 364 days was significantly higher in those treated with a maintenance dose of 160 mg compared with those treated with a maintenance dose of 80 mg (p=0.006). When the results for the different initial doses for each of the maintenance doses were combined the response rate was 76% (44/58) for 80 mg and 94% (49/52) for 160 mg. However, the results are unreliable as there was a statistically significant interaction between the initial dose and the maintenance dose (p=0.060), and a statistically significant initial dose effect (p=0.048). Consequently, the initial dose effect has biased the assessment of the maintenance dose effect. As a result of this bias, the maintenance effect no longer reflects just the effect of the maintenance dose but includes a significant component coming from the initial dose. The problem came from the 200/80 mg group in which a significant number of subjects failed to adequately respond at 28 days to the initial 200 mg dose (that is, testosterone levels > 0.5 ng/mL) and were subsequently included in the analysis as non-responders to the 80 mg maintenance dose. It is considered that the results for the maintenance dose comparison using the Day 28 to Day 364 (or Day 196) suppression data are unreliable and should be given no evidentiary weight.

Co-Primary Efficacy Endpoint – Suppression from 28 to 364 days in patients suppressed at Day 28.

The proportion of patients with serum testosterone concentrations ≤ 0.5 ng/mL from Day 28 to Day 364 for patients with serum testosterone concentrations ≤ 0.5 ng/mL at Day 28 are provided below in Table 11. This analysis has the effect of mitigating the "bias" arising from poor response to the initial 200 mg dose in the 200/80 mg group as only patients who were suppressed at Day 28 were included in the analysis. The proportion of patients suppressed from Day 28 to Day 364 was 92%, 96%, and 100% for the respective maintenance doses of 80 mg, 120 mg, 160 mg. The difference between the highest and lowest maintenance dose was statistically significant. The absolute difference (pairwise analysis) in response rates between the 80 mg and 160 mg maintenance doses was also statistically significant: 8.33% [95% CI: 0, 20%], p=0.04.

Table 11: Proportion of patients with testosterone ≤ 0.5 ng/mL from Day 28 to Day 364 for patients with testosterone ≤ 0.5 ng/mL at Day 28, ITT Completers [CS12].

	N	n	Response	95% CI
Initial doses combined/80 mg	48	44	92%	80 – 98%
Initial doses combined/120 mg	50	48	96%	86 – 100%
Initial doses combined/160 mg	49	49	100%	93 – 100%
Statistics: Maintenance dose effect: Odds Ratio (160/80 mg) = 10.3 [95% CI: 0.882, 287.649], p=0.066				

N: Number of patients in the analysis set and serum testosterone ≤ 0.5 ng/mL at Day 28.
n: Number of patients with all serum testosterone measurements ≤ 0.5 ng/mL from Day 28 to Day 364
Response % : n/N x 100

Secondary Efficacy Endpoints

Results for selected *secondary efficacy endpoints* were: for the 240 mg pooled group the proportion of patients with testosterone (≤ 0.5 ng/mL) at Day 28 was 95% (n=87/92) and for the 200 mg pooled group was 86% (n=81/94), p=0.089; there was rapid suppression of testosterone in all treatment groups with suppression at Day 3 ranging from 83-94% across the six treatment groups; for the 147 patients with testosterone suppression at Day 364 (that is, 78.6% of all patients treated with at least one dose of degarelix) the median level was 0.121 ng/mL; testosterone was maintained at low levels (~ 0.2 ng/mL) to Day 364 in all treatment groups; time to 90% reduction in baseline PSA levels was 56 days in all treatment groups except 200/80 mg where it was 84 days; median reduction in PSA compared with baseline at 12 weeks was similar for the treatment groups (93-96%); there was a rapid fall in LH levels in all treatment groups with median reductions from baseline at Day 1 being ≥ 80% and maximum reductions of ~ 90% occurring on Day 28; reduction in FSH levels was maintained throughout the study with median reductions from baseline in the 147 subjects with LH measurements at Day 364 being 92-95%; the fall in FSH levels was not as rapid as for LH with median reductions from baseline at Day 3 ranging from 36-39% but similar maximum reductions of ~ 90% on Day 28; LH levels gradually increased from maximum reductions at Day 28 to median reductions from baseline at Day 364 being 76-78% in the 146 patients with Day 364 measurements.

Comment

The study adopted a suppression response rate of 95% in the treated patients as being "adequate". Consequently, only the 120 mg and 160 mg doses maintained adequate suppression (≥ 95%) from Day 28 to 364 days in patients suppressed at Day 28. The response for the 80 mg dose (92%) is considered to be inadequate. Testosterone suppression at 28 days was higher in patients treated with an initial dose of 240 mg (95%) compared with 200 mg (86%), p=0.089. The study provides supportive evidence for the efficacy of an initial dose of 240 mg but not for 200 mg, and supportive evidence for the efficacy of maintenance doses of 120 mg and 160 mg but not for 80 mg.

Study CS14 – Efficacy Results

Co-Primary Efficacy Endpoint – Suppression from 28 to 364 days

The proportion of patients with testosterone level ≤ 0.5 ng/mL from Day 28 to Day 364 for the two treatments is provided below in Table 12. The initial dose was the same for both treatment groups (200 mg) while the maintenance doses were 60 mg or 80 mg. The generalised linear model (GLM) used to analyse the data included a factor for maintenance dose. The results showed that response rate for the 200/60 mg group was higher than for the 200/80 mg group, but that the difference was not statistically significant (maintenance effect, odds ratio). Similarly, the absolute difference (pairwise analysis) between the two treatment groups was not statistically significant: -8.36% [95% CI: -24%, 7%], p=0.327. The lower response in the 200/80 mg group was due to a larger number of patients randomised to that group not being suppressed by the initial dose of 200 mg. Consequently, there was an imbalance between the two groups at Day 28 in the number of patients suppressed even though all patients had received the same initial 200 mg dose.

Table 12: Proportion of patients with testosterone level ≤ 0.5 ng/mL from Day 28 to Day 364, ITT completers analysis [CS14].

Treatment Group	N	n	Response	95% CI
200/60 mg (Initial/Maintenance)	49	42	86%	73 – 94%
200/80 mg	53	41	77%	64 – 88%

(Initial/Maintenance)				
Statistics	Maintenance dose effect: Odds Ratio = 0.57 [95% CI: 0.173, 1.764], p =0.408			

N: Number of patients in the analysis set and serum testosterone ≤ 0.5 ng/mL at Day 28.
n: Number of patients with all serum testosterone measurements ≤ 0.5 ng/mL from Day 28 to Day 364
Response % : n/N x 100

Co-Primary Efficacy Endpoint – Suppression from 28 to 364 days in patients suppressed at Day 28.

The proportion of patients with serum testosterone concentrations ≤ 0.5 ng/mL from Day 28 to Day 364 for patients with serum testosterone concentrations ≤ 0.5 ng/mL at Day 28 is provided below in Table 13. The results showed that the response rate for the 80 mg maintenance dose was greater than for the 60 mg maintenance dose, but the difference was not statistically significant (maintenance effect, odds ratio). Similarly, the absolute difference (pairwise analysis) in the response rates between the treatment groups was not statistically significant: 4.29% [95% CI: -7%, 17%], p=0.557.

Table 13: Proportion of patients with testosterone level ≤ 0.5 ng/mL from Day 28 to Day 364 for patients with testosterone ≤ 0.5 ng/mL at Day 28, in the ITT completers analysis set [CS14].

Treatment Group	N	n	Response	95% CI
200/60 mg (Initial/Maintenance)	45	42	93%	82 – 99%
200/80 mg (Initial/Maintenance)	42	41	98%	87 – 100%
Statistics	Maintenance dose effect: Odds Ratio = 2.90 [95% CI: 0.222,157.423], p = 0.669			

N: Number of patients in the analysis set and serum testosterone ≤ 0.5 ng/mL at Day 28.
n: Number of patients with all serum testosterone measurements ≤ 0.5 ng/mL from Day 28 to Day 364.
Response % : n/N x 100

Secondary Efficacy Endpoints

Results for selected endpoints were: the pooled data for the 200 mg starting dose showed that the proportion of patients suppressed at Day 28 was 88% [95% CI: 81-93%]; the proportion of patients with testosterone levels ≤ 0.5 ng/mL at Day 3 was 93% for the 200/60 mg group and 83% for the 200/80 mg group (p=0.073); the median time to 50% and 90% reduction in PSA was 14 and 56 respectively for both treatment groups; and reductions from baseline to Day 364 were similar for both groups for testosterone, LH, DHT, FSH, and PSA

Comment

The study provides supportive evidence for adequate testosterone suppression (≥ 95% of patients) from 28 to 364 days for the 80 mg maintenance dose in patients who are suppressed at Day 28. The response rate seen with the 60 mg maintenance dose is considered to be inadequate. The efficacy of a 200 mg starting dose is not supported as the proportion of patients suppressed at Day 28 was less than 95% in the pooled data.

Other Studies

The results from *study CS02* in patients with prostate cancer are not directly relevant to the submission as the treatment regimen differed from that being proposed. In this study, treatment was administered on days 0, 3, and 28 with maintenance treatment every 28 days for a total duration of 24 weeks. The investigated regimens (Day 1/Day 2/maintenance) were 80/80/40, 40/40/40, and 40/-/40. The PP was the primary population for the assessment of efficacy. The primary efficacy endpoint required the lower 95% CI of the percentage of patients with serum testosterone concentrations < 0.5 ng/mL at Week 1 from initial dosing to

be at least 70%, and then to be least 90% at Weeks 2, 4, 8, 12, 16, 20, and 24. The 80/80/40 treatment regimen was the most effective of the three treatment regimens in reducing and maintaining testosterone suppression. However, all three treatment regimens failed to meet the primary efficacy endpoint in the PP.

Supportive Studies – Starting Dose – Studies CS07 and CS15

The *primary objective* of *study CS07* was to investigate the effects of ascending single doses of degarelix on testosterone suppression in patients with prostate cancer. The *primary objective* of *study CS15* was to establish whether treatment with degarelix could suppress serum testosterone levels (≤0.5 ng/mL) for 12 to 13 months in at least 80% of patients with prostate cancer. In study CS07, *secondary efficacy objectives* included assessment of the effects of SC degarelix on DHT, LH, FSH, and PSA. In *study CS15*, secondary efficacy endpoints included assessment of testosterone and PSA response for up to 12 or 13 months of treatment and time to disease progression. *Design* in *study CS07* was single-dose, multi-centre, open-label, ascending-dose, with parallel and sequential groups. *Design i*n s*tudy CS15* was repeat-dose, multi-centre, open-label, randomised, with parallel groups.

In *study CS07*, patients were allocated to one of eight single doses. These were: 120 mg (40 mg/mL); 120 mg (20 mg/mL); 160 mg (40 mg/mL); 200 mg (40 mg/mL); 200 mg (60 mg/mL); 240 mg (40 mg/mL); 240 mg (60 mg/mL); and 320 (60 mg/mL). The single 240 mg (40 mg/mL) dose was identical to the starting dose being proposed for registration. In *study CS15*, patients were randomised to one of three treatment groups with treatment being initiated with a starting dose (240 mg) followed by maintenance doses (240 mg) at 3 month intervals. The three regimens (starting dose/maintenance dose) were: Group A 240 mg (40 mg/mL)/240 mg (40 mg/mL) at months 1, 3, 6, 9; Group B 240 mg (40 mg/mL)/240 mg (60 mg/ml) at months 1, 3, 6, 9; and Group C 240 mg (40 mg/mL)/240 mg (60 mg/mL) at months 1, 4, 7, 10 months. The starting dose regimen of 240 mg (40 mg/mL) was identical to the starting dose being proposed for registration. The efficacy evaluation of *studies CS07 and CS15* centres on the results for the 240 mg (40 mg/mL) starting doses as the maintenance dose regimens were significantly different from that proposed for registration.

The inclusion and exclusion criteria were similar for both studies, and were consistent with those described previously for studies *CS12* and *CS14*. The major difference between the inclusion criteria for *studies CS07* and *CS15* was that patients were required to have life expectancies of 6 and 13 months, respectively.

Patients

In *study CS07*, 211 patients were screened, 180 were randomised to one of the eight dose groups, and 172 received degarelix. Of the 180 randomised patients, 153 completed the study and 27 were withdrawn (11 due to unsatisfactory PSA response, 3 due to AEs, and 13 for other reasons). The demographics of the 172 patients treated with degarelix (ITT analysis set) were mean age 79 years [range 48, 89], mean height 1.73 m [range 1.53, 1.73], mean weight 78.4 kg [range 28, 117] and mean BMI 25.7 kg/m^2 [range 18.8, 38.3]. All patients were Caucasian. The demographic characteristics of the treatment groups were similar.

In *study* CS15, 600 patients were screened, 460 were randomised to one of the three dose groups, and 447 received degarelix. Of the 460 randomised patients, 374 completed the study and 86 were withdrawn (33 due to AEs and 53 for other reasons). The demographics of the 447 patients treated with degarelix (ITT analysis set) were mean age 73.4 years [range 49, 90], mean height 1.73 m [range 1.46, 1.90], mean weight 78.1 kg [range 45, 133] and mean BMI 26.0 kg/m^2 [range 15.8, 44.6]. The patients were 91% white, 7% blacks of African heritage, and 3% other. The demographic characteristics of the treatment groups were similar.

Primary and Secondary Efficacy Endpoints

The *primary efficacy endpoint* in *study CS07* was the time from dosing until the serum testosterone concentration was > 0.5 ng/mL. In *study CS15*, the *primary efficacy endpoint* was the proportion of patients with serum testosterone concentrations ≤ 0.5 ng/mL from Day 28 until the end of the study. As this endpoint assessed the maintenance effect of dosing regimens significantly different from that being proposed for registration it will not be discussed further. However, *study CS15* included an analysis of the proportion of patients with testosterone concentrations ≤ 0.5 ng/mL at Day 28 after an initial dose of 240 mg (40 mg/mL) which is identical to the starting dose proposed for registration.

In *study CS07, secondary efficacy endpoints* included measurement of PSA, DHT, LH, FSH and SHBG. In *study CS15*, in addition to the secondary endpoint related to testosterone suppression at 28 days, other relevant 28 Day endpoints included PSA suppression and changes in LH and FSH concentrations.

Statistical Methods and Sample Size

In *study CS07*, the primary endpoint was analysed in the *ITT* and *PP analyses sets.* The *ITT analysis set* included all patients who received degarelix and had post-baseline testosterone and degarelix plasma concentration data. Time from dosing until testosterone was > 0.5 ng/mL was analysed using Kaplan-Meier survival estimates with the log-rank test being used to compare treatment groups. No formal estimates of *sample size* were made. In *study CS15*, statistical analysis and sample size were based on the primary efficacy endpoint which is not directly relevant to the proposed dosing regimen.

Study CS07 – Efficacy Results

Primary Efficacy Endpoint – Time to Testosterone Escape (> 0.5 ng/mL)

The results for the Kaplan-Meier estimates of median time from dosing until serum testosterone concentration > 0.5 ng/mL (ITT and PP analyses) and insufficient testosterone response (ITT analysis) are provided below in Table 14. The number of subjects in each treatment group in the ITT analysis set was 12 for 120 mg (40 mg/mL) and 160 mg (40 mg/mL); 24 for 200 mg (40 mg/mL), 200 mg (60 mg/mL), 240 mg (40 mg/mL) and 240 mg (60 mg/mL); 25 for 320 (60 mg/mL); and 27 for 320 mg (60 mg/mL). The difference among the doses for each of the analyses was highly statistically significant. The most efficacious dose for all three analyses was 240 mg/mL (40 mg/mL) (n=24).

Table 14: Kaplan-Meier Estimate of median time to first value > 0.5 ng/mL at Day 28+ (ITT, PP analyses) and median time to insufficient testosterone response (ITT analysis) [CS07].

Treatment Group	First value > 0.5 ng/mL at Day 28+ (ITT analysis set)	First value > 0.5 ng/mL at Day 28+ (PP analysis set)	Insufficiency Criterion [1] (ITT analysis set).
120 mg (20 mg/mL)	84 [63-119]	84 [63-119]	84 [70-119]
120 mg (40 mg/mL)	63 [28-133]	63 [28-133]	84 [14-133]
160 mg (40 mg/mL)	70 [28 – 98]	70 [28-98]	70 [14- 98]
200 mg (40 mg/mL)	140 [112-147]	140 [112-147]	140 [112-147]
200 mg (60 mg/mL)	84 [35-112]	84 [35-112]	84 [49-112]
240 mg (40 mg/mL)	140 [112-182]	140 [112-161]	161 [133-188]
240 mg (60 mg/mL)	88 [28-140]	84 [28-133]	109 [14-147]
320 mg (60 mg/mL)	133 [91-154]	133 [91-154]	147 [98-161]
Log-Rank Test	p = 0.0000586	p = 0.000137	$p = 9.7E^{-7}$

[1] Insufficient Testosterone Response: one testosterone value > 1.0 ng/mL or two consecutive testosterone values > 0.5 ng/mL

Secondary Efficacy Endpoints

Results for selected secondary efficacy endpoints included: median time to serum testosterone ≤ 0.5 ng/mL ranged from 1 to 2 days across all groups; percentage of observed cases with serum testosterone ≤ 0.5 ng/mL at Day 28 ≥ 95% seen only for 200 mg (40 mg/mL) [100%, 24/24] and 240 (40 mg/mL) [95.7%, 22/24]; and estimated median time to 50% reduction from baseline in PSA ranged from 14 to 21 days across all groups.

Comment

Based on the results for the primary and secondary endpoints relating to serum testosterone suppression, doses of 200 mg (40 mg/mL) and 240 mg (40 mg/mL) were the most efficacious as measured by response rates ≥ 95%. The study provides supportive evidence for the efficacy of the proposed initial dose of 240 mg (40 mg/mL).

Study CS15 – Efficacy Results

Secondary Endpoint – Pharmacodynamic – Serum testosterone (≤ 0.5 ng/mL) at Day 28

There was a high response rate at 28 days for 240 mg (40 mg/mL) ranging from 97% to 98% (Table 15, below).

Table 15: Proportion of patients with testosterone ≤ 0.5 ng/mL at Day 28, ITT analysis set [CS15].

	N	n	Response %	95% CI
240 mg (40 mg/mL) - Group A	146	142	97.3%	93 – 99
240 mg (40 mg/mL) - Group B	146	143	97.9%	94 – 100
240 mg (40 mg/mL) - Group C	145	142	97.9%	94 – 100

N: Number of patients with testosterone value. n: Number of patients with serum testosterone ≤ 0.5 ng/mL.

Other Secondary Pharmacodynamic Endpoints

Selected results for the secondary endpoints at Day 28 after 240 mg (40 mg/mL) include: median reductions in PSA ranged from 79% to 83%; serum LH levels markedly reduced with mean reductions from baseline ranging from 96% to 97%; serum FSH levels markedly reduced with mean reductions from baseline ranging from 91% to 93%; serum SHBG remained constant throughout the study; and FAI reflected changes in serum testosterone levels

Comment

This study showed that a singe dose 240 mg (40 mg/mL) was highly effective in reducing serum testosterone concentration at Day 28. The study provides supportive evidence for the efficacy of the initial proposed dose of 240 mg (40 mg/mL).

Other Studies

In addition to *studies CS07* and *CS15*, *study CS12* (discussed above) also provides supportive evidence for the efficacy of the proposed starting dose. A further study [CS06] investigated the effects of single SC doses of degarelix on testosterone suppression in patients with prostate cancer. However, the doses (40, 80, 120, 160 mg) were different from the proposed starting dose. Consequently, this study is considered to be not directly relevant to efficacy. Furthermore, the proportion of patients with serum testosterone concentrations ≤ 0.5 ng/mL at Day 28 did not exceed 80% for any of the four doses tested.

Pivotal Study – CS21

This pivotal study compared the efficacy and safety of two SC degarelix treatment regimens and an IM leuprolide 7.5 mg treatment regimen administered every 28 days for up to 12 months in patients with prostate cancer. The two degarelix regimens were both initiated with a dose of 240 mg (40 mg/mL) followed 28 days later by a maintenance dose of either 160 mg (40 mg/mL) or 80 mg (20 mg/mL) repeated every 28 days. The *primary objective* was to demonstrate that degarelix could effectively achieve and maintain testosterone suppression to castration levels (≤ 0.5 ng/mL) during 12 months treatment. The *secondary objectives* were to compare serum levels of testosterone and PSA during the first 28 days of treatment; to compare the safety and tolerability of the treatment regimens; to compare testosterone LH, FSH, and PSA response during the entire treatment period; to compare patient reported outcomes (Quality of Life and hot flushes); and to evaluate the PK of the degarelix dosing regimens. The *study design* was multi-centre, open-label, randomised, stratified, active-controlled, and parallel group. It included patients from 11 countries from three geographical regions; the Americas (44 centres), Central and Eastern Europe (31 centres), and Western Europe (7 centres). The study was initiated on 07 February 2006 (first patient, first visit) and was completed on 08 October 2007 (last patient, last visit). The total duration of the study was 20 months. The database was locked on 18 October 2007, but re-opened on 26 October 2007 to remove a patient from the PP randomised to leuprolide but erroneously treated with degarelix.

A total of 620 patients were randomised 1:1:1 to one of three treatment groups. Of these 620 patients, 610 received treatment and 10 withdrew before dosing. Patients were stratified according to geographic region (Central and Eastern Europe, Western Europe, and the Americas) and body weight (< 90 kg and ≥ 90 kg). In the two degarelix treatment groups, patients received a starting dose of 240 mg (40 mg/mL) administered SC on Day 0 as two equivalent SC injections of 120 mg (ie 2x 3 mL). Thereafter, these patients received 12 additional single degarelix doses of either 80 mg (20 mg/mL) or 160 mg (40 mg/mL) administered SC (1x 4 mL) every 28 days. In the third treatment group, patients received active treatment with leuprolide 7.5 mg on Day 0 and then every 28 days as a single IM injection. At the investigator's discretion, patients treated with leuprolide 7.5 mg could also be given bicalutamide to protect against testosterone flare. The protocol specified that degarelix was to be given as a deep SC injection on the abdominal wall using a 45 degree injection angle with specific instructions that the injection site not be massaged. The three treatment groups were designated D240/80 (ie 240 mg starting dose followed by 80 mg maintenance dose every 28 days), D240/160 (ie 240 mg starting dose followed by 160 mg maintenance dose every 28 days), and L7.5 (ie 7.5 mg every 28 days).

Comment

Treatments were administered open-label. Double-dummy administration would have been required to blind both subjects and investigators to treatments due to SC and IM administration. The open-label design had the potential to bias reporting of adverse events (AEs) against degarelix as investigators would have been familiar with the AE profile of leuprolide but not with degarelix resulting in hypervigilance for AEs associated with the new product. The primary and most of the secondary efficacy endpoints were based on objective biochemical measurements making assessment bias highly unlikely. The laboratory personnel were blinded to treatment and the sponsor's personnel were blinded to the results of the hormone assays during the main part of the study. The subjects were randomised to treatment by a centralised computerised procedure which would have prevented allocation bias. The degarelix starting and maintenance doses were based on the results of the Phase II studies and are considered to be appropriate and justified. The 240 mg (40 mg/mL) starting dose of degarelix followed by 80 mg (20 mg/mL) maintenance dose regimen included in the pivotal study is identical to that being proposed for registration as regards dose, concentration, number of injections, volume of injections and method of manufacture of the formulation (LPPS). The IM leuprolide 7.5 mg active control was manufactured by TAP Pharmaceuticals (USA) with the trade name Lupron Depot 7.5 mg. There is a similar product registered in Australia called Lucrin Depot sponsored by Abbott and indicated for "the palliative treatment of metastatic or locally extensive prostatic cancer (stages C and D)" at an IM dose of 7.5 mg monthly. Information from public domain documents (Lupron Depot 7.5 mg US package insert and Lucrin Depot Australian PI) suggests that the formulations of the two products are identical or at least very similar. The active leuprolide control used in the pivotal study is considered appropriate in the context of Australian medical practice

Inclusion and Exclusion Criteria

The study included patients aged≥ 18 years with histologically confirmed (Gleason graded) adenocarcinoma of the prostate (all stages), in whom androgen ablation treatment, except for neoadjuvant hormonal therapy, was indicated. This included patients with rising PSA after having undergone prostatectomy or radiotherapy with curative intention. At screening, the serum testosterone concentration was required to be > 1.5 ng/mL and the PSA ≥ 2 mg/mL. In addition, patients were required to have an ECOG score ≤ 2 and a life expectancy of at least 12 months. Exclusion criteria included previous or concurrent hormonal management of prostate cancer. However, patients who had undergone prostatectomy or radiotherapy with curative intention and neoadjuvant/adjuvant hormonal therapy could be enrolled provided the neoadjuvant/adjuvant hormonal therapy had a maximal duration of 6 months and had been terminated at least 6 months prior to screening. If a patient experienced disease progression during the study (for example, increased clinical signs and symptoms, or rising PSA) treatments for prostate cancer were allowed, other than prostatectomy, or treatment with GnRH receptor agonists or GnRH antagonists. All patients were required to have had a bone scan and current T staging (classification according to TNM [tumour, nodule, and metastatic] system) within the 12 weeks before start of treatment, and these data had to be available before randomisation. Patients were excluded if considered candidates for curative therapy. Patients with hepatic or symptomatic biliary disease were excluded as were patients with alanine aminotransferase ALT or bilirubin levels > the upper level of normal range (ULN).

Study Subjects

After randomisation, the population of the three treatment groups was D240/60 (n=206), D240/80 mg (n=210), and L7.5 (n=204). The completion and discontinuation rates in randomised patients (n=620) were 81% (n=504) and 19% (n=116), respectively. Non-fatal

AEs accounted for 4% (n=27) of discontinuations, while fatal AEs during and after treatment accounted for 3% (n=18) and < 1% (n=1) of discontinuations, respectively. Lack of testosterone suppression accounted for discontinuation of only 2 patients (< 1%). Only 6 patients (<1%) were lost to follow.

Comment

The overall completion rate of 81% was satisfactory, and the proportion of patients lost to follow-up was small (<1%). Discontinuations occurred more frequently in the two D treatment groups (20-21%) than in the L7.5 group (16%). The difference appeared to be primarily due to more frequent discontinuations due to non fatal AEs in the two D treatment groups (5-7%) compared with the L7.5 group (1%). Discontinuations due to non fatal AEs (n=27) occurred more frequently in randomised patients from the Americas (6.4%, n=17) than from Central and Eastern Europe (2.3%, n=8). Discontinuations due to AEs occurred more frequently in patients weighing < 90 kg (81.4%, n=22) than patients weighing≥ 90 kg (18.6%, n=5).

Of the 620 randomised patients, 610 received at least one treatment dose and were included in the ITT analysis set. Of the 10 randomised patients who did not receive treatments, 2 withdrew consent, 1 took a prohibited medicine, 4 were erroneously randomised, 2 did not meet inclusion/exclusion criteria, and 1 experienced a delay in drug administration. Of the 610 patients in the ITT analysis set, randomisation to the three treatments were: D240/160 (n=202), D240/80 mg (n=207), and L7.5 (n=201). The mean (SD) demographics of the 610 randomised patients were: age 72.0 (8.45) years; height 1.72 (0.068) m; weight 79.3 (13.4) kg and BMI 26.8 (3.93) kg/m^2. The majority of patients were white (84%), with the remainder being American Indian or Alaska native (10%), black of African heritage (6%) and Asian (< 1%). The basic demographic factors were similar for the three treatment groups.

At the time of enrolment, of the 610 patients in the ITT analysis set, 31% (n=191) had localised cancer, 29% (n=178) had locally advanced cancer, 20% (n=125) had metastatic cancer, and 19% (n=116) had non-classifiable disease. Overall, the prostate cancer characteristics were similar for the treatment groups. However, locally advanced cancer was more prevalent in the D treatment groups (31% each) compared with the L7.5 group (26%). The mean time since prostate cancer diagnosis was 491 days [range 62-6585] and was similar for the three treatment groups as were previous therapies.

Nearly all patients in the ITT population (89%) had a history of other medical conditions in addition to prostate cancer. The most common disorders, other than non-renal and urinary disorders, were hypertension (52%), hypercholesterolaemia (16%) and myocardial ischaemia (12%). Overall, the medical histories were similar for patients in the three treatment groups, although the L7.5 group had a higher proportion of patients with reproductive system and breast disorders (31%), mainly benign prostatic hypertrophy (BPH) and prostatism, than the D treatment groups (both 23%). In addition, the D240/160 group had a lower proportion of patients with gastrointestinal disorders than the D240/80 or L7.5 groups (25%, 34%, and 31%, respectively). Of the ITT population, 72% (n=441) were on concomitant medications during the study. These medications were predominantly anti-hypertensives, lipid lowering agents, anti-thrombotics, antiinflammatories, diuretics, and drugs for "cardiac therapy". Patients in all treatment groups who developed signs of disease progression could be treated with anti-androgen therapy (apart from GnRH antagonists or agonists). Overall, patients with prostate cancer in the ITT population are considered to be representative of those for whom ADT might be offered as a treatment option.

Primary Efficacy Endpoint

The *primary efficacy endpoint* was the probability of testosterone levels≤ 0.5 ng/mL from Day 28 to Day 364. Two hypotheses were tested to assess the efficacy of degarelix. A *degarelix response rate* estimation determined whether the lower bound of the 95% confidence interval (CI) for the cumulative probability of testosterone≤ 0.5 ng/ml from Day

28 to Day 364 was no lower than 90% (FDA criterion). In other words, efficacy would be demonstrated if the cumulative response rate was at least 90% with a 95% probability. A *non-inferiority assessment* based on the lower bound of the 97.5% CI determined whether degarelix was non-inferior to leuprolide 7.5 mg with respect to the cumulative probability of testosterone ≤ 0.5 ng/mL from Day 28 to Day 364. The non-inferiority limit (lower bound of the 97.5% CI) for the difference between treatments (each degarelix regimen versus leuprolide 7.5 mg) was specified to be -10 % (European Medicines Agency [EMEA] criterion). The CI (97.5%) was adjusted using the Bonferroni method in order to maintain an overall type 1 error of 5% resulting in the significance level for each of the two pairwise comparisons being 2.5%.

Comment

The primary efficacy endpoint of testosterone suppression to levels ≥ 0.5 ng/mL is considered to be acceptable. This level is supported by the literature [Lepor, 2005], and appears to have been the castration threshold for the studies supporting Australian registration of leuprolide for the palliative treatment of advanced prostate cancer [leuprolide PI]. The 90% efficacy response for the proportion of patients achieving castration levels is considered to be acceptable. The proportion of patients achieving castration levels (serum testosterone≤ 0.5 ng/mL) at 28 days has been shown to be ≥ 90% for a number of GnRH antagonists with rates being maintained for up to 52 weeks [Lepor, 2005].

Secondary Efficacy Endpoints

There were a number of secondary efficacy endpoints including the proportion of patients with testosterone surge in the first 2 weeks of treatment; changes in testosterone suppression over time; changes in LH, FSH, PSA over time; and changes in quality of life. Standard and acceptable statistical methods were used to analyse the secondary endpoints.

Statistical Analysis and Sample Size

The *primary efficacy endpoint* of cumulative probability of testosterone≤ 0.5 ng/mL from Day 28 to Day 364 was estimated by the *Kaplan-Meier method*. Testosterone levels were measured at discrete time-points before dosing from Day 28 (± 2 days) and then every 28 days (± 7 days) through to and including Day 364. Testosterone response rates with 95% confidence intervals (CI) were calculated by log-log transformation of survivor function for each of the treatment groups. The primary efficacy endpoint was analysed in both the ITT and PP populations, with the ITT population being considered primary.

Sample size and power calculations were based on the FDA and EMEA criteria for analysis of the primary efficacy endpoint, and an estimate (based on previous studies) that both degarelix treatment regimens would achieve testosterone suppression rates of approximately 96%. With 200 patients for each D group, power would be 90% to show that the lower limit of the 95% CI was ≥ 90% (FDA criterion), assuming a 96% testosterone suppression response rate and a drop-out rate of 15%. With 200 patients for each treatment group, power would be > 90% to show non-inferiority of D versus L7.5 with respect to the probability of testosterone levels ≤ 0.5 ng/mL from Day 28 to Day 364 (EMEA criterion), assuming a 96% testosterone suppression response rate and a non-inferiority margin of -10%, a two-sided significance level of 2.5% and a drop-out rate of 15%.

Comment

In the original protocol, the primary endpoint was the proportion of patients with testosterone levels ≤ 0.5 ng/mL from Day 28 through Day 364 analysed for the observed cases in the ITT and PP analysis sets with the PP analysis set being considered primary. The original protocol

specified that the effectiveness of degarelix was to be demonstrated by showing non-inferiority to leuprolide with respect to the proportion of patients with testosterone ≤ 0.5 ng/mL from Day 28 to 364 with the non-inferiority limit for the difference between treatments (each degarelix regime versus L7.5) to be -10% (lower bound limit of 97.5% CI). However, the original protocol was amended on 14 February 2006 in order to accommodate requests from the FDA and the EMEA to modify the statistical methods. The effect of these modification resulted in two formal statistical analyses being performed, one assessing the degarelix response versus a pre-determined threshold of success and one assessing the non-inferiority of degarelix versus leuprolide. The amendments to the sponsor's Statistical Analysis Plan (SAP) were finalised on 28 February 2006 before the first patient received the first dose.

However, the Kaplan-Meier method of analysis of the primary efficacy endpoint was not specified in the original protocol (or amendments) or in the finalised SAP. This analytical method appears to have been adopted after collection of the data. The original pre-specified analysis of the primary end point was interval-censored life-table estimation of time to first testosterone escape. However, the sponsor considered this to be an inappropriate method of analysis since the time to actual testosterone escape between scheduled visits was not measured and the primary endpoint was suppression of testosterone values at discrete 28 day intervals from Day 28 to Day 364 (inclusive). The sponsor considered that the interval-censored life-table method would require daily or even continuous testosterone measurements in order to accurately assess time to escape. Consequently, as testosterone suppression was measured at discrete 28 day time points the sponsor considered the appropriate analytical method to be product-limit estimate of survival (that is, the Kaplan-Meier method). The sponsor did not incorporate the changed analytical method into a protocol amendment as it considered that the overall statistical methodology was "still survival analysis" and that "the principal features of the analysis as laid out in the protocol and SAP is intact". Furthermore, it argued that "as the Kaplan-Meier method is slightly more conservative than the interval-censored life-table method due to the way censored patients are handled, and testosterone values are blinded to the sponsor, it was not considered necessary to amend the protocol". While the circumstances relating to the protocol amendments and modifications to the statistical analytical method are unusual they are considered acceptable and do not compromise the validity of the study.

Results – Primary Efficacy Endpoints

Degarelix was shown to be efficacious in achieving and maintaining serum testosterone concentration ≤ 0.5 ng/mL (that is, castration levels) in the ITT and PP analysis sets. For each of the three treatments, the lower bound 95% CI for the cumulative probability of testosterone suppression from Day 28 to Day 364 was ≥ 90%. In addition, the lower bound 97.5% CI for the difference in response between degarelix (both doses) and leuprolide was greater than the specified non-inferiority limit of -10%. The results for the ITT analyses are summarised below in Table 16.

Table 16: Cumulative probability of testosterone suppression (≤ 0.5 ng/mL) from Day 28 to Day 364 – ITT analysis set [CS21].

Degarelix 240/160 mg			Degarelix 240/80 mg			Leuprolide 7.5 mg		
N	C	Cumulative	N	C	Cumulative	N	C	Cumulative
202	199	Probability	207	202	Probability	201	194	Probability
		98.3%			97.2%			96.4%
		[95% CI: 94.8,			[95% CI: 93.5,			[95% CI: 92.5,

99.4]	98.8]	98.2]
Difference D vs L	Difference D vs L	
1.9%	0.9%	-
[97.5% CI: -1.8, 5.7]	[97.5% CI: -3.2, 5.0]	-

N = patients in ITT analysis set. C = number of censored observations at or before Day 364. Difference = difference in response rate between D and L. Within-treatment group 95% CI calculated by log-log transformation of the survivor function. Between-group 97.5% calculated by normal approximation using pooled standard error; non-inferiority margin for the difference between D and L is -10%.

A number of sensitivity analyses were performed to establish whether the conclusions drawn from the primary analysis were robust. Estimates of the probability of testosterone≤ 0.5 ng/mL from Day 28 to Day 364 in the ITT analysis based on geographical region and weight were undertaken and were > 90% for most of the groups, however, the lower bound 95% CI was not ≥ 90% for all groups. In order to account for missing testosterone values, a Cox-proportional hazard analysis using testosterone monitoring frequency (that is, the number of missing testosterone values/treatment months) as a covariate was undertaken. The results of this sensitivity analysis showed that testosterone monitoring frequency did not have a significant effect on the primary efficacy analysis. Response rate (proportion of patients with testosterone ≤ 0.5 ng/mL from Day 28 to Day 364) was also analysed using observed cases (defined as patients who either completed the study or had a testosterone measurement of > 0.5 ng/mL at Day 28 and onwards). The response rates for the observed case analyses (ITT population) were: 98.2% [95% CI: 94.7, 99.6%] for D 240/160; 97.0% [95% CI: 93.2, 99.0%] for D240/80; and 96.0% [95% CI: 91.8, 98.4%] for L7.5. The difference between D240/160 and L7.5 was 2.2% [97.5% CI: -1.4, 5.8], and between D240/80 and L7.5 was 1.1% [97.5% CI: -2.8, 5.0]. The observed cases method provided a conservative estimate of the response rate at Day 364 because patients with testosterone values ≤ 0.5 ng/mL who withdrew early were not carried forward. The results for the observed cases analysis were similar to those for the Kaplan-Meier analysis.

Comment

The results for the primary analysis showed that both D240/160 and D240/80 treatment regimens were effective in suppressing testosterone from Day 28 to Day 364. The results also showed that both D240/160 and D240/80 treatment regimens were non-inferior to L7.5 in suppressing testosterone from Day 28 to Day 364. Overall, the sensitivity analyses supported the robustness of the primary Kaplan-Meier analysis.

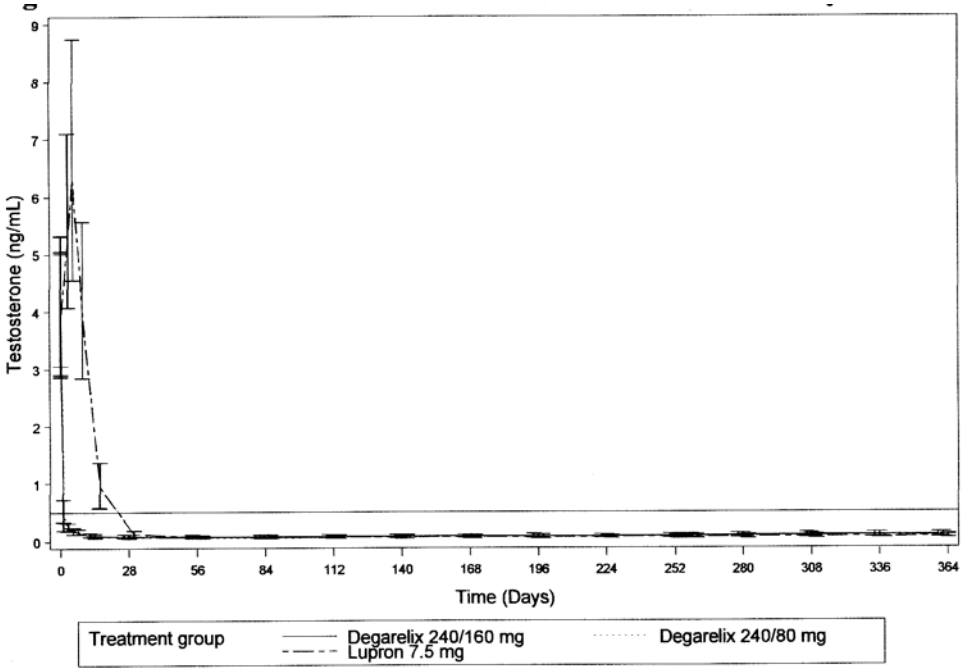
Results – Secondary Efficacy Endpoints

Testosterone Surge First 2 Weeks of Treatment: Testosterone surge was defined as the testosterone level exceeding baseline by≥ 15% on any 2 days during the first 2 weeks of treatment. If one or more of the testosterone values on Days 1, 3, 7 or 14 was missing, the last observation was carried forward. The proportion of patients with testosterone surge during the first 2 weeks of treatment in the ITT analysis set was: 0.5% [95% CI: 0.0, 2.7%] for D 240/160 (1 of 202 patients); 0% [95% CI: 0.0, 1.8] for D240/80 (0 of 207 patients); and 80.1% [95% CI: 73.9, 85.4] for L7.5 (161 of 201 patients); $p < 0.001$ for D vs L for each D group separately and combined. In the L7.5 group, the proportion of patients who had a testosterone surge during the first 2 weeks of treatment was lower in patients who started anti-androgen therapy before or on Day 7 (72.7%), compared with those who did not use anti-androgen therapy (80.9%).

Testosterone ≤ 0.5 ng/mL at Day 3: The proportion of patients with testosterone levels≤ 0.5 ng/mL at Day 3 in the ITT analysis set was: 95.5% [95% CI: 91.7, 97.9] for D240/160 (193 of 202 patients); 96.1% [95% CI: 92.5, 98.3] for D240/80 (199 of 207 patients); and 0%

[95%CI: 0.0, 1.8] for L7.5 (0 of 201 patients); $p < 0.001$ for D vs L for each D group separately and combined. Median testosterone levels at Day 3 were 0.36, 0.25, and 6.30 ng/mL for D240/160, D240/80 and L7.5, respectively. The levels for both D groups remained suppressed through to the end of the study, while those for L began dropping to reach a suppressed level by Day 28 after which levels remained suppressed until the end of the study. The testosterone levels over time profiles are provided in Figure 4.

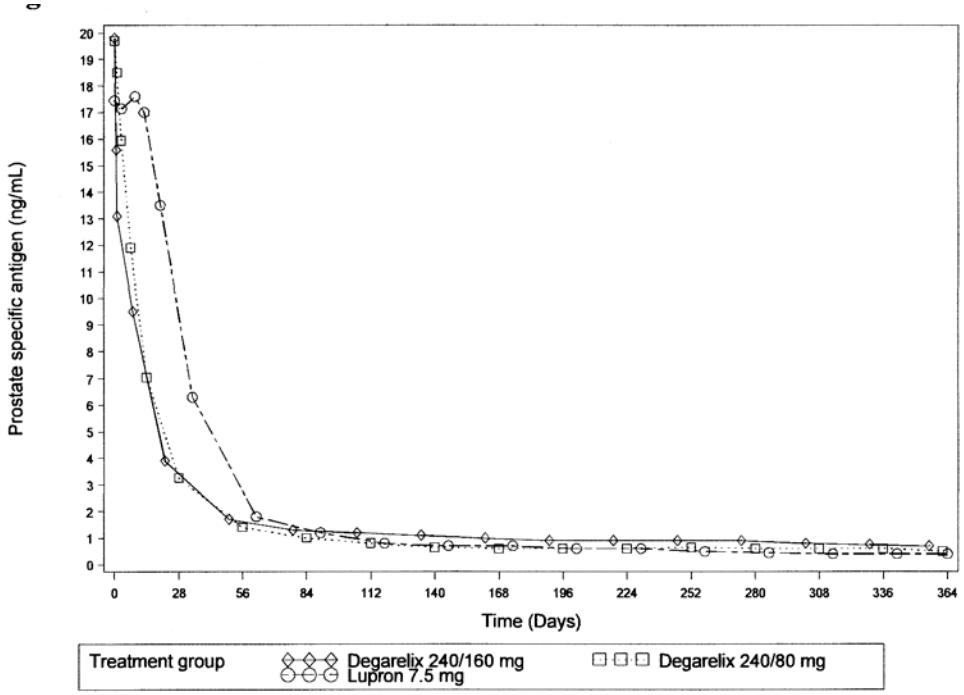
Figure 4: Median testosterone levels over time – ITT analysis [CS21].



Sufficient Testosterone Response Day 28-364: Insufficient testosterone response was defined as one testosterone value > 1.0 ng/mL, or two consecutive values > 0.5 ng/mL taken 28 days apart from Day 28 to 364. Sufficient testosterone response from Day 28 to Day 364 was 98.8%, 97.8% and 96.9% for D240/160, D240/80 and L7.5, respectively. The lower limit of the 97.5% CI of the difference between both D groups and L was greater than the -10% non-inferiority margin. The median testosterone concentration and median change from baseline at Day 364 were, respectively: for D240/160 (n=162), 0.100 ng/mL [interquartile range P25-P75: 0.064, 0.150] and -3.86 ng/mL; for D240/80 mg (n=167), 0.087 ng/mL [interquartile range P25-P75: 0.060, 0.150] and -4.08 ng/mL; for L7.5 (n=170), 0.074 ng/mL [interquartile range P25-P75: 0.051, 0.110] and -3.85 ng/mL.

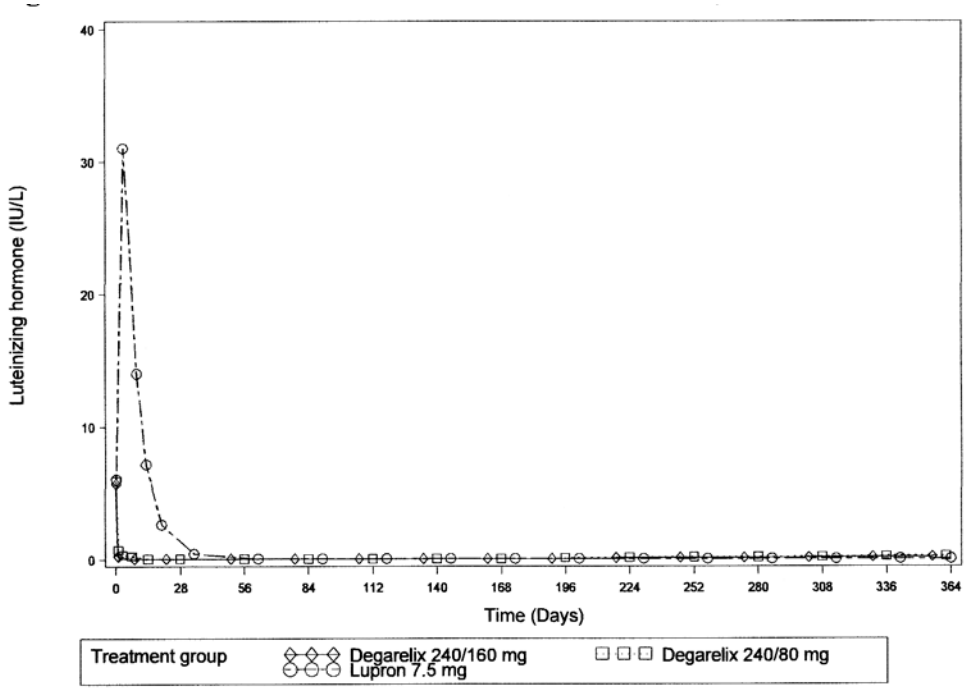
PSA: On Day 14, the *median percentage changes in PSA* from baseline were -64.6%, -63.4% and -17.9% for D240/160, D240/80 and L7.5, respectively, in the ITT analysis. The respective values on Day 28 were -82.3%, -84.9%, and -66.7%. Results at days 14 and 28 for the D vs L comparisons were statistically significant ($p<0.001$). In the L7.5 group, a greater median percentage reduction from baseline in PSA at Day 14 was observed in patients who started anti-androgen therapy on or before Day 7 (-61.7%) compared with those not treated with anti-androgen therapy (-15.3%). The respective figures on Day 28 were -81.9% and -61.7%. The median percentage reductions in PSA at Day 14 and Day 28 in patients treated with L7.5 and anti-androgen therapy were similar to those seen in patients treated with D. *PSA failure* was 13%, 8% and 13% for D240/160, D240/80 and L7.5, respectively. Approximately 50% of PSA failures for each treatment group were observed by Day 224. Time to PSA failure was defined as the day from first dosing when an increase in serum PSA ≥ 50% from nadir and at least 5 ng/mL was measured on 2 consecutive occasions at least 2 weeks apart. The second occasion was the time-point for the criterion. The PSA levels over time profiles are provided in Figure 5.

Figure 5: Median PSA levels over time – ITT analysis [CS21].



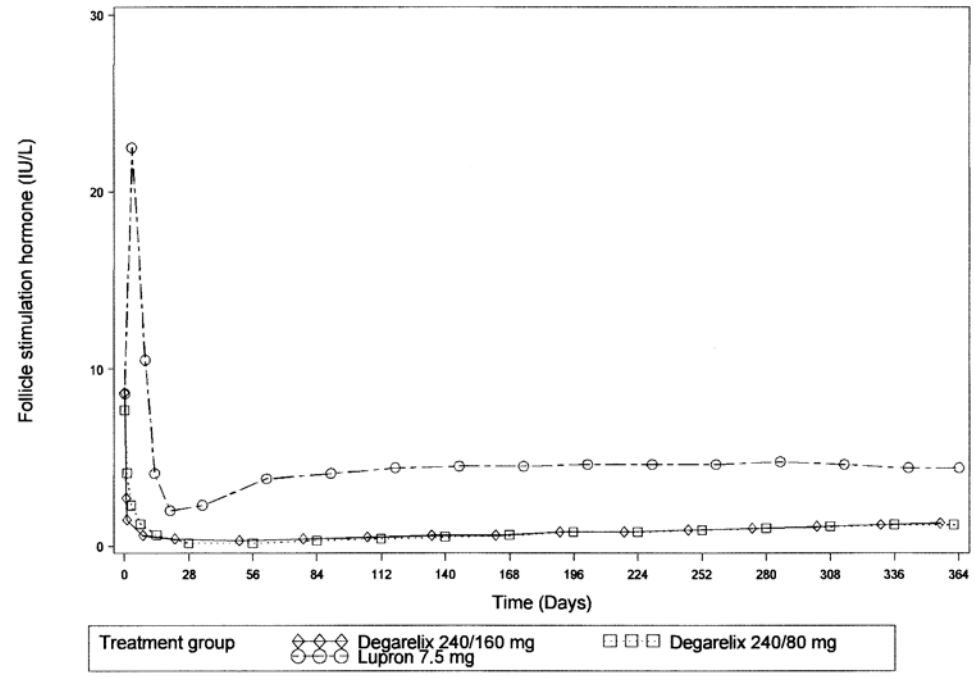
LH and FSH : The profiles for *serum levels of LH over time* were similar to those observed for testosterone. After degarelix, median LH levels decreased rapidly from baseline with reductions to levels of < 0.7 IU/L (~88% reduction from baseline) being observed on Day 1 after which median levels remained suppressed until Day 364. In contrast, after leuprolide there was an initial surge in LH levels peaking on Day 1 with a level of 31.0 IU/L (> 400% increase from baseline) before falling to 0.035 IU/L on Day 56 and remaining at about this level until Day 364. Median serum LH profiles over time are provided in Figure 6.

Figure 6: Median LH levels over time – ITT analysis [CS21].



There was also a *rapid fall in FSH levels* after degarelix with reductions to ≤ 1.5 IU/L (> 80% reduction from baseline) by Day 7 with levels then remaining suppressed until Day 364. In contrast, after leuprolide there was an initial surge in FSH levels peaking on Day 1 with a level of 22.5 IU/L (146 % increase from baseline) before falling to 2.0 IU/L by Day 14 after which there was an increase in levels to about Day 56 after which levels remained relatively constant at about 4.40 IU/L. Median FSH profiles over time are provided in Figure 7.

Figure 7: Median FSH levels over time – ITT analysis [CS21].



Testosterone Microsurges: Testosterone levels on Day 255 and/or Day 259 were compared with levels on Day 252 (that is, the day of the 10th injection) in order to see whether increases (microsurges) occurred shortly after injection. In leuprolide treated patients, 5 had

testosterone microsurges of 0.25-0.5 ng/mL and 3 had microsurges of > 0.5 ng/mL. No microsurges were seen in degarelix treated patients. Whether microsurges occurred after injection at other time points is unknown. The clinical significance of microsurges is unknown but surges to testosterone levels ≤ 0.5 ng/mL are unlikely to be clinically significant.

Quality of Life: There were methodological problems associated with collection of the quality of life (QoL) data relating to the electronic transfer of results and patient compliance. The available data showed no differences among the three treatment groups in QoL, and no changes in QoL over the course of the study. However, the lack of a placebo comparator and the presence of methodological problems means that no meaningful conclusions can be made about the effect of treatment on QoL.

Hot Flushes: The daily frequency and severity of hot flushes over the course of the study were measured using patient diaries with ratings from mild (=1) to very severe (=4). There were methodological problems associated with collection of the data similar to those experienced for QoL. The irregularly collected data suggested no change in the median number of severe and very severe hot flushes per day. The frequency and severity of hot flushes were similar for the three treatment groups.

MRI Scan: A sub-study was planned to assess tumour size by magnetic resonance imaging (MRI) before and after treatment in approximately 45 patients. However, only 2 patients had pre- and post-treatment MRI scans. Consequently, no conclusions can be drawn from this sub-study.

Sub-group Analyses

Apart from the investigation of efficacy in the population stratified by geographical location and weight there were no other sub-group analyses in the study. The sponsor's Clinical Summary of Efficacy (CSE) "included [*post-hoc* sub-group analyses] for the sake of description and not for hypothesis testing since none of the studies were powered to this end". These exploratory subgroup analyses (age, race, region, stage of prostate cancer, weight) undertaken in the CSE have not been evaluated.

Effect of Anti-degarelix Antibodies

The study included an assessment of the effect of anti-degarelix antibodies on efficacy. Of the patients treated with the 80 mg maintenance dose, 10% (n=17/169) were antibody positive at 12 months.

Safety

Exposure

The submission included the sponsor's Summary of Clinical Safety (SCS) which examined relevant degarelix safety data from one and three month treatment regimen studies in patients with prostate cancer, studies in healthy males included in the prostate development program, and studies in females investigating the use of degarelix for the treatment of infertility. The evaluation of safety in the clinical evaluation centres on patients with prostate cancer. In particular, attention has been given to the data from the pivotal Phase III study [CS21], and from the combined Phase II/III one month treatment regimen studies (of which the data from [CS21] is a sub-set).

In the *Phase II/III studies (1 & 3 month regimens)*, 1836 patients (2153 person-years) were exposed to degarelix. In these studies, 1334 patients were exposed to degarelix for ≥ 6 months and 1148 for ≥ 12 months. In the *Phase II/III studies (1 month regimen)*, 1256 patients (1514 person-years) were exposed to degarelix and 201 patients (178 person-years)

were exposed to leuprolide. In these studies, 921 patients were exposed to degarelix for ≥ 6 months and 755 for ≥ 12 months. Patient exposure data for the prostate cancer program are provided in Table 17. In the *pivotal Phase III study [CS21*], 202 patients were treated with D240/160 for a mean time of 11.0 months [range 0.3, 12.4], 207 with D240/80 for a mean time of 10.9 months [range 0.3, 12.5], and 201 with L7.5 for a mean time of 11.2 months [range 0, 12.8]. Cumulative exposure to degarelix was > 1,000 mg for about 89% of the exposed patients (n=409), and > 2,000 mg for about 40% of the exposed patients.

Table 17: Summary of number of unique subjects/patients and person-years exposure by dosing regimen in the degarelix development program.

Study Groups	Treatment Groups	
	Degarelix N (person years)	**Placebo N (person years)**
Phase 1 Clinical Pharmacology in Healthy Male Volunteers	138 (28.0)	26 (4.49)
	Degarelix N (person years)	**Leuprolide 7.5 mg N (person years)**
Phase 2/3 Prostate Cancer Indication One-Month Dosing Regimen		
Active Controlled Phase 3	409 (354)	201 (178)
Uncontrolled Phase 2/3	1090 (1365)	NA
Phase 2/3 Total	1256 (1514)	201 (178)
Phase 2/3 Prostate Cancer Indication – All Studies		
Active Controlled Phase 3	409 (354)	201 (178)
Uncontrolled Phase 2/3	1670 (2004)	NA
Phase 2/3 Total	1836 (2153)	201 (178)

Note: Since patients in CS21 and CS21A are in the uncontrolled study-group as well as the active controlled study-group, the total number of patients in the Phase 2/3 Total study groups is less than their sum. Patients on leuprolide 7.5 mg, switching to degarelix in CS21A are double-counted in the Phase 2/3 total. There were 132 patients who switched.

Patient Disposition

Patient disposition data for the *Phase II/III studies (1 month regimen)* are provided below in Table 18 (see note under that table for explanation of apparent discrepancy in figures). In the *pivotal study [CS21]*, completion rates were high for both degarelix treated patients (81%) and leuprolide treated patients (86%). AEs accounted for 8% of discontinuations in degarelix treated patients and 6% in leuprolide treated patients. The main AE imbalance between the two groups was for non-fatal AEs with the difference being primarily due to more frequent injection site reactions with degarelix. The discontinuation rate in the *uncontrolled Phase II/III studies (1 month regimen)* for degarelix was high (42%) with lack of testosterone suppression accounting for 14%. Degarelix doses used in early uncontrolled studies were too low to adequately suppress testosterone.

Table 18: Disposition of patients in Phase II/III Studies (Main and Extension) for degarelix one-month dosing regimen.

	Phase 3 Controlled		Phase 2/3 Uncontrolled	Total
	Degarelix	Leuprolide 7.5 mg	Degarelix	Degarelix
Exposed Patients	409	201	1090	1256[1]
Completed	332 (81%)	172 (86%)	168 (15%)	257 (20%)
Ongoing	0	0	459 (42%)	459 (37%)
Discontinued	77 (19%)	29 (14%)	463 (42%)	540 (43%)
Reason for discontinuation				
Adverse Event	34 (8%)	12 (6%)	111 (10%)	145 (12%)
Non fatal event	24 (6%)	3 (1%)	63 (6%)	87 (7%)
Fatal during treatment	9 (2%)	9 (4%)	36 (3%)	45 (4%)
Fatal post treatment	1 (<1%)	0	12 (1%)	13 (1%)
Lack of PSA suppression[2]	2 (<1%)	0	84 (8%)	86 (7%)
Lack of testosterone suppression[2]	0	0	148 (14%)	148 (12%)
Lost to follow-up	5 (1%)	1 (<1%)	6 (<1%)	11 (<1%)
Other	36 (9%)	16 (8%)	114 (10%)	150 (12%)

[1] Includes 1124 from the main studies and 132 patients who received degarelix in CS21A after receiving leuprolide in CS21.

[2] Forced withdrawal as per protocol in studies CS02/A, CS06/A, CS07/A, CS12/A, CS14/A

Source: Module 2, SCS, Table 11, page 26.

Note, since 243 patients in CS21A are also counted in CS21 and since 132 receiving leuprolide in CS21 were later randomized to degarelix in CS21A, the total number of patients in the Phase II/III studies (1090 + 409 – 243) is less than the sum of the Phase II/III uncontrolled studies and Phase III active control study.

Adverse Events

Common Adverse Events

In the *Phase II/III studies (1 month regimen)*, 77% (n=972) of degarelix treated patients reported at least one adverse event (AE). A total of 14 AEs occurred with degarelix at an incidence of > 5%: hot flush (31%); injection site pain (18%); injection site erythema (11%); back pain (7%); fatigue (7%); nasopharyngitis (7%); weight increased (7%); urinary tract infection (6%); arthralgia (6%); ALT increased (6%); dizziness (6%); constipation (5.5%); hypertension (5.3%); and diarrhoea (5.3%).

In the *pivotal study [CS21]*, AEs occurred in 81% (n=330) of degarelix treated patients and 78% (n=156) of leuprolide treated patients. The following AEs (D vs L) occurred statistically significantly ($p \leq 0.5$) less frequently in degarelix treated patients than in leuprolide treated patients: musculoskeletal and connective tissue disorders (17% vs 26%); reproductive system and breast disorders (5% vs 10%); urinary tract infection (3% vs 9%); arthralgia (4% vs 9%); oedema peripheral (2% vs 5%); erectile dysfunction (1% vs 4%); chest pain (<1% vs 3%); cystitis non-infective (0% vs 2%); cardiac murmur (0% vs 1%); musculoskeletal stiffness (0% vs 1%); libido decreased (0% vs 1%); deep vein thrombosis (0% vs 1%); and myocardial ischaemia (<1% vs 2%). The following AEs (D vs L) occurred statistically significantly ($p \leq 0.05$) more frequently in degarelix treated patients than in leuprolide treated patients: general disorders and administrative site conditions (47% vs 18%); injection site pain (29% vs < 1%); injection site erythema (21% vs 0%); injection site swelling (7% vs 0%); injection site nodule (5% vs 0%); injection site induration (5% vs 0%); chills (4% vs 0%); injection site pruritus (3% vs 0%); injection site inflammation (3% vs 0%); injection site irritation (3% vs 0%); and influenza like illness (2% vs 0%). The AE profiles of the two degarelix dosing regimens were similar, apart from a higher incidence of injection site reactions with D240/160 than with D240/80. The AEs for the two degarelix regimens and the leuprolide regimen are summarised in Table 19 (System Organ Class [SOC]) and Table 20 (SOC and Preferred Term).

Injection Site Reactions

The method, number of injections, and volume of injection of the two products differed with degarelix being given as a SC injection starting dose (2 x 3 mL) followed by a maintenance

dose (1 x 4 mL) compared with IM leuprolide (1 x 1 mL). These differences are reflected in the different AE injection site reactions of the two products. In the *pivotal study [CS21]*, injection site reactions occurred in 40% (n=162) of degarelix treated patients compared with < 1% (n=1) in leuprolide treated patients ($p \leq 0.001$). Not surprisingly, two or more injection site reactions occurred simultaneously in many degarelix treated patients. The majority of injection site AEs (80%) did not require any treatment, while those requiring treatment (20%) were treated mainly with over-the-counter (OTC) medication (~ 50%) or cold packs (~ 20%). The incidence of injection site reactions was higher with D240/160 than with D240/80 (44% [n=73] vs 35% [n=36]). Most of the degarelix injection site reactions were reported in the first month after the initial dose (34% [n=68] for D240/160 vs 32% [n=66] for D240/80]. The incidence of injection site reactions was more common following the first 5 doses with D240/160 than with D240/80 after which the incidence was similar for the two treatment regimens. Most of the reactions were rated as mild to moderate by the patient and investigator. Three injection site reactions were considered to be of clinical importance in the context of 16,000 administered injections. Overall, the incidence of injection site reactions in degarelix treated patients was 4.4 per 100 injections, and the two most common reactions were injection site pain (2.9 per 100 injections) and injection site erythema (1.9 per 100 injections).

Table 19: Summary of adverse events by system organ class – ITT analysis set [CS21].

MedDRA System Organ Class	Treatment Group: Degarelix 240/160 mg		Degarelix 240/80 mg		Degarelix Total		Leuprolide 7.5 mg	
	N	(%)	N	(%)	N	(%)	N	(%)
ITT analysis set	202	(100%)	207	(100%)	409	(100%)	201	(100%)
Treatment-emergent adverse events	167	(83%)	163	(79%)	330	(81%)	156	(78%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	11	(5%)	5	(2%)	16	(4%)	12	(6%)
CARDIAC DISORDERS	19	(9%)	17	(8%)	36	(9%)	27	(13%)
CONGENITAL, FAMILIAL & GENETIC DISORDERS							1	(<1%)
EAR & LABYRINTH DISORDERS	3	(1%)	6	(3%)	9	(2%)	3	(1%)
ENDOCRINE DISORDERS	2	(<1%)			2	(<1%)	3	(1%)
EYE DISORDERS	4	(2%)	6	(3%)	10	(2%)	5	(2%)
GASTROINTESTINAL DISORDERS	33	(16%)	38	(18%)	71	(17%)	39	(19%)
GENERAL DISORDERS & ADMINISTRATION SITE CONDITIONS	102	(50%)	92	(44%)	194	(47%)	36	(18%)
HEPATOBILIARY DISORDERS	2	(<1%)	2	(<1%)	4	(<1%)	3	(1%)
IMMUNE SYSTEM DISORDERS	1	(<1%)	1	(<1%)	2	(<1%)		
INFECTIONS & INFESTATIONS	38	(19%)	45	(22%)	83	(20%)	49	(24%)
INJURY, POISONING & PROCEDURAL COMPLICATIONS	11	(5%)	10	(5%)	21	(5%)	17	(8%)
INVESTIGATIONS	58	(29%)	54	(26%)	112	(27%)	62	(31%)
METABOLISM & NUTRITION DISORDERS	26	(13%)	14	(7%)	40	(10%)	15	(7%)
MUSCULOSKELETAL & CONNECTIVE TISSUE DISORDERS	37	(18%)	31	(15%)	68	(17%)	53	(26%)
NEOPLASMS BENIGN, MALIGNANT & UNSPECIFIED (INCL CYSTS AND POLYPS)	12	(6%)	10	(5%)	22	(5%)	16	(8%)
NERVOUS SYSTEM DISORDERS	27	(13%)	24	(12%)	51	(12%)	23	(11%)
PSYCHIATRIC DISORDERS	16	(8%)	16	(8%)	32	(8%)	21	(10%)
RENAL & URINARY DISORDERS	26	(13%)	28	(14%)	54	(13%)	39	(19%)
REPRODUCTIVE SYSTEM & BREAST DISORDERS	13	(6%)	9	(4%)	22	(5%)	21	(10%)
RESPIRATORY, THORACIC & MEDIASTINAL DISORDERS	17	(8%)	25	(12%)	42	(10%)	18	(9%)
SKIN & SUBCUTANEOUS TISSUE DISORDERS	21	(10%)	18	(9%)	39	(10%)	10	(5%)
SURGICAL & MEDICAL PROCEDURES	2	(<1%)			2	(<1%)		
VASCULAR DISORDERS	65	(32%)	71	(34%)	136	(33%)	60	(30%)

Intensity of Adverse Events

In the *pivotal study [CS21]*, AE intensity was graded according to the Common Toxicity Criteria for Adverse Events (CTCAE) system. This system grades AEs on a scale of 1-5 with grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (life-threatening/disabling) and grade 5 (death). Most of the AEs in both treatment groups were rated as mild or moderate. Mild AEs occurred in 69% (283/409) of degarelix treated patients and 69% (138/201) of leuprolide treated patients. Moderate AEs occurred in 55% (225/409) of degarelix treated patients and 50 % of leuprolide treated patients (101/201). Severe AEs occurred in 17% (68/409) of degarelix treated patients and 13% (26/201) of leuprolide treated patients. Life threatening AEs occurred in 1.4% (3/209) of degarelix treated patients (4 events – 1 x anaemia, 1 x pain, 1 x diabetes mellitus, 1 x cerebrovascular accident), and 2.5% (5/201) of leuprolide treated patients (7 events – 2 x anaemia, 1 x ventricular arrhythmia, 1 x large intestinal obstruction, 1 x cerebrovascular accident, 1 x hypoxic encephalopathy, 1 x respiratory failure). Death occurred in 2.4% (10/409) of degarelix treated patients and 4.5% (9/201) of leuprolide treated patients.

Table 20: Adverse events by system organ class and preferred term occurring in≥5% of any treatment group –ITT analysis set [CS21].

MedDRA System Organ Class/ Preferred Term	Treatment Group: Degarelix 240/160 mg N	(%)	Degarelix 240/80 mg N	(%)	Degarelix Total N	(%)	Leuprolide 7.5 mg N	(%)
ITT analysis set	202	(100%)	207	(100%)	409	(100%)	201	(100%)
Treatment-emergent adverse events	167	(83%)	163	(79%)	330	(81%)	156	(78%)
GASTROINTESTINAL DISORDERS	33	(16%)	38	(18%)	71	(17%)	39	(19%)
Nausea	11	(5%)	9	(4%)	20	(5%)	8	(4%)
Constipation	6	(3%)	11	(5%)	17	(4%)	10	(5%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	102	(50%)	92	(44%)	194	(47%)	36	(18%)
Injection site pain	61	(30%)	58	(28%)	119	(29%)	1	(<1%)
Injection site erythema	48	(24%)	36	(17%)	84	(21%)		
Injection site swelling	14	(7%)	13	(6%)	27	(7%)		
Fatigue	13	(6%)	7	(3%)	20	(5%)	13	(6%)
Injection site induration	11	(5%)	8	(4%)	19	(5%)		
Injection site nodule	13	(6%)	6	(3%)	19	(5%)		
Chills	7	(3%)	11	(5%)	18	(4%)		
INFECTIONS AND INFESTATIONS	38	(19%)	45	(22%)	83	(20%)	49	(24%)
Urinary tract infection	3	(1%)	10	(5%)	13	(3%)	18	(9%)
INVESTIGATIONS	58	(29%)	54	(26%)	112	(27%)	62	(31%)
Weight increased	22	(11%)	18	(9%)	40	(10%)	24	(12%)
Alanine aminotransferase increased	17	(8%)	20	(10%)	37	(9%)	11	(5%)
Aspartate aminotransferase increased	10	(5%)	11	(5%)	21	(5%)	6	(3%)
METABOLISM AND NUTRITION DISORDERS	26	(13%)	14	(7%)	40	(10%)	15	(7%)
Hypercholesterolaemia	12	(6%)	7	(3%)	19	(5%)	5	(2%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	37	(18%)	31	(15%)	68	(17%)	53	(26%)
Back pain	12	(6%)	12	(6%)	24	(6%)	17	(8%)
Arthralgia	6	(3%)	11	(5%)	17	(4%)	18	(9%)
VASCULAR DISORDERS	65	(32%)	71	(34%)	136	(33%)	60	(30%)
Hot flush	52	(26%)	53	(26%)	105	(26%)	43	(21%)
Hypertension	14	(7%)	12	(6%)	26	(6%)	8	(4%)

Time Dependency of Common Adverse Events

In the *pivotal study [CS21]*, the incidence of the most common AEs remained relatively stable over the first 13 months of treatment for both degarelix and leuprolide. However, the incidence of injection site pain and erythema after degarelix decreased following peaks of 24% and 17% in the first month, respectively, to 0% and <1%, respectively, at 11-13 months. The incidence of hot flushes after degarelix also decreased over 13 months from a peak of 15% in the first month to 1% at 11-13 months. Similarly, hot flushes after leuprolide decreased from a peak of 12% at 2-4 months to 2% at 11-13 months. The incidence of hot flushes after leuprolide at 2-4 months (12%) was greater than that at 1 month (8%). This most likely reflects the delay in testosterone suppression seen with leuprolide. The incidence of weight gain increased after degarelix from < 1% in the first month to 9% at 11-13 months, and a similar increase was seen after leuprolide from 0% in the first month to 10% at 11-13 months.

Long-Term Exposure and Adverse Events

The main Phase II/III one-month regimen long-term extension studies are still on-going but safety data from these studies were included at the database cut-off date of 28 September 2007 (CS12A, CS14, CS21A). Three other extension studies were terminated before the database cut-off date due to low and ineffective doses of degarelix [CS02A, CS06A, CS07A]. In the total degarelix safety database (n=1836), 63% (n=1148) of patients have been exposed to the drug for at least 12 months, 24% (n=434) for at least 24 months, and 8% (n=153) for at

least 36 months. In the *Phase II/III studies (1 month regimen)* (n=1256), the patient discontinuation rate for most AEs associated with degarelix remained relatively stable when assessed over 6 month intervals (3-4%) to 24 months and then increased after 24 months (13%). However, after 24 months the assessment period was longer than 6 months which might at least partially account for the increased number of discontinuations observed after 24 months.

In the *Phase II/III studies (1 month regimen)*, the *incidences* of the most common AEs were relatively constant for each of the 3 month observation periods to month 24. At month > 24, it appears that the incidences of the AEs increase but this is because the number of exposed patients is low and this time interval encompasses more than one 3 month interval. Injection site pain, injection site erythema, and hot flushes, have the greatest incidence at 1-3 months after which incidence decreases and stabilises over time. In contrast, the incidence of weight increase was higher at 13-15 months (5%) than at 1-3 months (<1%).

In the *Phase II/III studies (1 month regimen)*, the *prevalences* of the most common AEs were relatively stable over time. The prevalences at month > 24 appear greater for the same reasons given above for the incidences. The prevalence at 22-24 months was greater than at 1-3 months for hot flush (40% vs 26%), fatigue (8% vs 4%), arthralgia (7% to 2%), and hypertension (5% vs 1%). Similarly, the prevalence of weight increase was lower at 1-3 months (< 1%) than at 19-21 months (8%). In contrast, for injection site pain (2% vs 13%) and injection site erythema (1% to 9%) the prevalence at 22-24 months was lower than at 1-3 months

Adverse Drug Reactions

Adverse drug reactions (ADRs) were defined as AEs considered by the investigators to be possibly or probably related to the drug. In the *Phase II/III studies (1 month regimen)*, 57% (n=718) of degarelix treated patents were considered to have experienced an ADR. The most common degarelix ADRs (≥ 5%) were: hot flushes (31%); injection site pain (17%), injection site erythema (11%); and fatigue (5%). In the *pivotal study [CS21]*, 58% (n=238) of degarelix treated patients were considered to have experienced an ADR compared with 42% (n=84) of leuprolide treated patients. The most common ADRs (≥ 5%) associated with degarelix (vs leuprolide) were: injection site pain 29% (vs < 1%); hot flushes 26% (vs 21%); injection site erythema 20% (vs 0%); injection site swelling 7% (vs 0%); weight increased 7% (vs 7%); injection site nodule 5% (vs 0%); and ALT increased 6% (vs 2%).

Withdrawal and Rebound Adverse Events

The effect of discontinuation of degarelix was examined in a total of 615 patients from 4 studies [CS02A, CS07/CS07A, CS12/CS12A, CS14/CS14A]. In these studies, "withdrawal/rebound" AEs were reported in 54 (9%) patients with most occurring in only 1 or 2 patients. The only AEs occurring in 3 or 4 patients were constipation (n=4), pneumonia (n=3), urinary tract infection (n=3), diabetes mellitus (n=3) and cerebrovascular accident (n=3). The results suggest that AEs related to discontinuation of degarelix are unlikely to be clinically significant.

Serious Adverse Events (SAE)

In the *pivotal study [CS21]*, the incidence of SAEs was 11% (n=45) in degarelix treated patients and 14% (n=28) in leuprolide treated patients. SAEs occurring in more than 1 patient in the degarelix group (vs leuprolide) were: anaemia < 1% (vs 1%); cardiac arrest < 1% (vs 0%); inguinal hernia < 1% (vs 0%); bronchopneumonia < 1% (vs 0%); prostate cancer < 1% (vs < 1%); urinary retention < 1% (vs < 1%); haematuria < 1% (vs 0%); calculus bladder < 1% (vs 0%); and ureteric calculus < 1% (vs < 1%). The only SAE to occur in ≥ 3 patients in

the degarelix group was haematuria (n=3). SAEs occurring in more than 1 patient in the leuprolide group (vs degarelix) were: anaemia 1% (vs < 1%); and myocardial infarction < 1% (vs <1%). The only SAE occurring in≥ 3 patients in the leuprolide group was anaemia (n=3). Of the 45 SAEs reported with degarelix, 24 (12%) occurred with D240/160 and 21 (10%) with D240/80.

In the *Phase II/III studies (1 month regimen)*, the incidence of SAEs with degarelix was 18% (n=227). The most commonly occurring SAEs (≥ 5 patients) were: urinary retention (n=12); pneumonia (n=11); myocardial infarction (n=9); cerebrovascular accident (n=9); metastases to the bone (n=8); haematuria (n=7); inguinal hernia (n=7); cardiac failure (n=7); disease progression (n=7); prostate cancer (n=6); anaemia (n=6); chronic obstructive pulmonary disease (n=5); back pain (n=5); angina pectoris (n=5); and acute myocardial infarction (n=5).

Deaths

In the *Phase II/III studies (1&3 month regimens)*, there were 89 deaths (4.8%) in 1863 patients. There were no deaths in the Phase I studies in healthy male subjects or in subjects with hepatic impairment [CS01, CSO5, CS08, CS23]. In the *pivotal study [CS21]*, 19 deaths occurred during the course of the study (that is, on or before the end-of-study visit, or on or before the last visit with available data plus 45 days). Of these 19 deaths, 10 (2.4%) occurred with degarelix and 9 (4.5%) occurred with leuprolide. The respective mortality rates per 1000 person-years were 28.2 [95% CI: 13.5, 51.9] and 50.7 [95% CI: 23.2, 96.2], p=0.2945. Of the 10 degarelix deaths, 5 occurred in the D240/160 group and 5 in the D240/80 group. The causes of the 5 deaths in the D240/160 group were: prostate cancer; prostate cancer metastatic; cardiopulmonary failure; renal failure acute; and cardiac failure and bronchopneumonia. The causes of the 5 deaths in the D240/80 group were: cardiac arrest (x2); myocardial infarction; bronchopneumonia; and gastric haemorrhage. The causes of the 9 deaths in the L7.5 group were: prostate cancer; gallbladder cancer and duodenal ulcer haemorrhage; cardiovascular disorder; cardiac disorder; cardiopulmonary failure; cardiac failure; acute myocardial infarction; renal failure acute; and peritonitis. None of the deaths in the pivotal study were considered to be related to treatment.

In the *Phase II/III studies (1 month regimen)*, there were 65 deaths (5%) in 1256 degarelix treated patients with 1.51 person-years of exposure, and the estimated mortality per 1000 person-years was 43.0 [95% CI: 33.2, 54.8]. The most common causes of death (≥ 3 patients) were: myocardial infarction (n=5); disease progression (n=5); cardiac failure (n=3); cardio-respiratory arrest (n=3); cardiac arrest (n=3); cardio-pulmonary failure (n=3); bronchopneumonia (n=3); and prostate cancer (n=3). In the *uncontrolled Phase II/III studies (3 month regimen)*, there were 24 (4%) deaths in 580 degarelix treated patients with 0.639 person-years of exposure, and an estimated mortality per 1000 person-years of 37.5 [95% CI: 24.1, 55.9].

Adverse Events Resulting in Discontinuation

In the *pivotal study [CS21]*, the incidence of patient discontinuation was 9% with D240/160, 7% with D240/80, and 6 % with L7.5. AEs resulting in discontinuation in≥ 3 degarelix treated patients were injection site pain (n=3) and prostate cancer (n=4). There were a number of AEs reported with degarelix and resulting in discontinuation which were considered by investigators to be either possibly or probably drug related: 3x injection site pain; injection site reaction; injection site induration; depression; hot flush; PSA increased; prostate cancer; hepatic enzyme increased; and hypersensitivity.

In the *Phase II/III studies (1 month regimen)*, the incidence of AEs resulting in discontinuation in degarelix treated patients was 11%. The most common reasons (≥ 5

patients) were: prostate cancer (n=8); metastases to bone (n=5); cerebrovascular accident (n=5); injection site pain (n=7); disease progression (n=6); and myocardial infarction (n=5).

Cardiovascular Events

Androgen deprivation therapy has been associated with an increased risk of cardiovascular disease in older men. In view of this increased risk, the submission included an analysis of cardiovascular AEs (stroke, coronary artery disease, heart failure, myocardial failure, and sudden cardiac death). The incidence rates of these events in the *pivotal study [CS21]* were compared with the background incidence of these events in a cohort of men aged≥ 65 with prostate cancer (n=71,838) from the Surveillance Epidemiology End Results (SEER) Medicare linked database. In the pivotal study, the incidence rates per 1000 person years for coronary artery disease, heart failure, and myocardial infarction were lower in the degarelix group than in the leuprolide group, while the rates for stroke were higher in the degarelix group than in the leuprolide group. The highest crude incidence rates were seen for coronary artery disease in both the degarelix and leuprolide groups (3% vs 5%, respectively). The incidence rates per 1000 person years for each of the cardiovascular AEs were lower in the degarelix group than the background rates in the SEER cohort of patients with a history of GnRH therapy (n=22,705). Similarly, the incidence rates for cardiovascular AEs (apart from heart failure) were lower in the degarelix group than the background rates in the SEER cohort of patients with prostate cancer (n=71,838).

The submission also included an analysis of relevant AEs using MedDRA High Level Group Terms (HLGT) of *Central Nervous System Vascular Disorders*, *Cardiac Arrhythmias*, *Coronary Artery Disorders* and *Heart Failures*. In the *pivotal study [CS21]*, the incidences of *Cardiac Arrhythmias*, *Coronary Artery Disorders*, and *Heart Failures* were lower in the degarelix group than in the leuprolide group, while the incidence of *Central Nervous System Vascular Disorders* was higher in the degarelix group than in the leuprolide group. The highest crude incidence rates were seen for *Cardiac Arrhythmias* in both degarelix and leuprolide groups (5% vs 8%, respectively).

Comment

There appeared to be no increased risk of cardiovascular or cerebrovascular AEs in patients treated with degarelix in the clinical studies. The incidence of heart failure in patients treated with degarelix was higher than the background incidence in patients with prostate cancer (SEER database), but was lower than the background incidence in patients with prostate cancer treated with GnRH therapy (SEER database). Apart from stroke, the incidence of cardiovascular AEs was lower in degarelix treated patients than in leuprolide treated patients. However, the data are based largely on patients exposed to degarelix and leuprolide for less than 12 months. Consequently, the emergence of an increased risk of cardiovascular and cerebrovascular AEs after long-term (> 12 months) treatment with degarelix can not be excluded.

Hypersensitivity Adverse Events

The submission included a detailed assessment of hypersensitivity reactions associated with degarelix treatment. This assessment reflected concerns arising from the severe life-threatening hypersensitivity reactions seen with an earlier generation GnRH antagonist (abarelix). In the degarelix development program, all patients (apart from those in the first human study CS02) were monitored for at least 1 hour post-injection in order to detect any immediate hypersensitivity reactions (ie > 1700 patients observed on > 19,000 dosing occasions). Narrow and broad scope terms of the Standardised MedDRA Queries (SMQs) for anaphylactic reaction, angioedema, and severe cutaneous adverse reactions were used to

assess the risk of these events in patients exposed to degarelix. The narrow scope terms identified AEs that are likely to represent hypersensitivity reactions of major clinical significance (that is, anaphylactic reaction, angioedema, and severe cutaneous adverse reactions such as Stevens-Johnson Syndrome, toxic epidermal necrolysis, and erythema multiforme). The broad scope terms identified potential hypersensitivity reactions, but included many terms that may be due to conditions not indicative of a hypersensitivity type reaction. In the analyses, the dosing period (not number of patients) was used and was defined as the period from one dosing to the next.

In the *Phase II/III studies (1&3 month regimens)* there were a total of *10 narrowly defined hypersensitivity* reaction events reported in 1836 degarelix treated patients (0.5%), and 2 events in 201 leuprolide treated patients (1.0%). Of the 10 events reported in degarelix treated patients, 3 occurred within the first 24 hours after administration against a background of 23,148 dosing periods (incidence of 0.01%), and 7 occurred after 72 hours against a background of 22,368 dosing periods (incidence of 0.03%). In the *pivotal study [CS21]*, there was 1 narrowly defined hypersensitivity reaction event (generalised urticaria) reported with degarelix at 0-24 hours against a background of 4,861 dosing periods (incidence of 0.02%), and 4 events (2x urticaria, 1x angioedema, 1x swelling of the face) at > 72 hours against a background of 4,839 dosing period (incidence of 0.08%). The corresponding figures for leuprolide treated patients were 0 at 0-24 hours against a background of 2,444 dosing periods and 2 (1 x swollen tongue, 1 x urticaria) against a background of 2,429 dosing periods (incidence of 0.08%) at > 72 hours

The broad term analysis collected a total of more than 300 events from the prostate cancer studies making interpretation difficult. In the *pivotal study [CS21]***,** there were 68 broadly defined events after degarelix (13 at 0-24 hours, 1 at 24-48 hours, 3 at 48-72 hours, 51 at > 72 hours), and 35 after leuprolide (5, 3, 1, 26, in the respective time periods). The incidence of events per dosing period in the first 24 hours was 0.3% for degarelix (13 events in 4,861 dosing periods) and 0.2% for leuprolide (5 events in 2,444 dosing periods), with the corresponding values after 72 hours being 1.1% for both treatments.

Degarelix Antibodies

The submission included a report of a study evaluating the immunogenicity of degarelix. Overall, about 10% of patients became antibody positive after one years treatment with degarelix. The majority of patients with broadly defined hypersensitivity reaction events occurring later than 24 hours after dosing with antibody measurements were antibody negative.

Comment

There were no reports of anaphylaxis associated with injection of degarelix in more than 1700 patients after more than 19,000 dosing administrations. Similarly, there were no reports of severe cutaneous reactions with the drug. Overall, data from the pivotal study [CS12] suggest that there are no significant differences between the hypersensitivity reaction profiles of degarelix and leuprolide, irrespective of whether narrow or broad terms are used. The use of broad terms resulted in a large number of events being reported making interpretation difficult. The anti-degarelix antibody data suggest that there is no relationship between antibodies and hypersensitivity reactions. There was no apparent correlation between hypersensitivity reactions and eosinophil counts. The incidence of antibody formation after 1 year of treatment with degarelix was about 10%.

Clinical Laboratory Results

Haematology

Androgen deprivation has been shown to decrease haematocrit (Hct), haemoglobin (Hb), and red blood cell count (RBC). In the *pivotal study [CS21]*, the mean fall from baseline was 8.3 g/L after degarelix and 9.0 g/L after leuprolide, and falls to markedly abnormal Hb values of ≤ 115 g/L (normal range 130-180 g/L) occurred in 24% of degarelix treated patients and 27% of leuprolide treated patients. A shift in Hb from high/normal to low occurred in 40% of degarelix and 36% of leuprolide treated patients. The mean fall in Hct was 2.2% after degarelix and 2.5% after leuprolide, and falls to markedly abnormal Hct values (≤ 37%) occurred in 48% of degarelix treated patients and 51% of leuprolide treated patients. A shift in Hct from high/normal to low occurred in 39% of both degarelix and leuprolide treated patients. The mean fall in RBC (10^9/L) was 0.285 after degarelix and 0.334 after leuprolide, and falls to markedly abnormal RBC values (≤ 3.5) occurred in 14% of degarelix treated patients and 16% of leuprolide treated patients. A shift in RBC from high/normal to low occurred in 38% of degarelix and 46% of leuprolide treated patients. Anaemia was reported in 3% of degarelix and 5% of leuprolide treated patients, and was considered to be serious in 2 patients (<1%) treated with degarelix and 3 (<1%) treated with leuprolide. Overall, changes in WBC parameters were not marked and were similar for both drugs.

Biochemistry

Androgen deprivation therapy has been associated with changes in serum biochemistry parameters including increases in insulin levels and increases in glucose levels suggesting a decrease in insulin sensitivity and an increased risk of and exacerbation of diabetes mellitus. In addition, it has also been associated with increases in cholesterol and blood urea nitrogen. Reporting of results in this section focuses on the pivotal study [CS21].

Renal Function

In the *pivotal study [CS21]*, shifts in urea nitrogen from low/normal baseline levels to high levels at the last visit occurred in 68% of degarelix treated patients and 69% of leuprolide treated patients, with respective mean increases from baseline of 0.852 and 1.13 mmol/L, and respective markedly abnormal values (≥ 10.7 mmol/L) of 25% and 29%. However, changes in serum creatinine levels were much less marked suggesting that neither treatment significantly affects renal function. Increases in creatinine were reported as an AE in 0.5% (n=2) of degarelix treated patients and 1.0% (n=11) of leuprolide treated patients, with respective values for creatinine increases being 1.2% (n=5) and 2.0% (n=4).

Liver Function

Both degarelix and leuprolide were associated with abnormal liver function tests. However, there was no evidence that either drug induces severe liver damage. Overall, the effects of degarelix on liver function were similar to those of leuprolide. Treatment with both drugs resulted in increased ALT and aspartate aminotransferase (AST) levels which appeared to be without significant clinical consequence.

In the *pivotal study [CS21]*, the sponsor evaluated the liver function test (LFT) findings using guidance from the FDA's "Clinical White Paper" [November 2000]. In this paper the FDA reviewed strategies to detect drugs with serious hepatotoxic potential and drew attention to the importance of increased transaminase levels combined with increased bilirubin levels as a predictor of serious liver injury (that is, Hy's Law). In October 2007, the FDA published a "Draft Guidance For Industry" on "Drug-Induced Liver Injury: Pre-marketing Clinical Evaluation". The strategies in the draft document built on those in the "Clinical White Paper" and once again stressed the importance of Hy's law in detecting severe drug induced liver injury (ie liver injury causing death or transplantation). The sponsor focused on ALT (ULN specified as 25 IU/L) and bilirubin (ULN specified as 18.8 mmol/L) as the main markers of liver impairment. The focus on ALT rather than AST is acceptable as it is more specific for hepatic injury. The sponsor used the following LFT categories to assess the effect of treatment on liver function: ALT > 3x ULN with concurrent total bilirubin increased >1.5x or >2x ULN; elevations of ALT or AST classified as 1-3x ULN, 3-5x ULN, 5-10x ULN, and >10x ULN; and elevations of bilirubin between 1-1.5x ULN, 1.5-2.0x ULN and >2x ULN.

There were no patients in the study with an ALT ≥ 3x ULN and a bilirubin ≥ 1.5x ULN. However, increased ALT levels to > 3x ULN occurred in 6.8% (n=28) of degarelix treated patients and 6.0% (n=12) of leuprolide treated patients, with respective levels > 5x ULN occurring in 0.98% (n=4) and 0.99% (n=2), and levels of > 10x ULN occurring in 0.49% (n=2) and 0%. There was a similar pattern of increases seen for AST. Shifts from baseline levels of low/normal to high at last visit occurred in 44% of degarelix treated patients and 45% of leuprolide treated patients with the respective figure for AST being 37% for both treatments. Increases in ALT reported as an AE occurred in 9% (n=37) of degarelix treated patients and 6% (n=11) of leuprolide treated patients, with respective figures for AST being 5% and 3 %. None of the increases in ALT or AST reported as AEs were classified as serious and none resulted in withdrawal from the study. Increases in ALT were generally reversible.

However, there were a few cases where reversibility could not be determined due to results being unavailable. ALT levels considered to be ADRs were reported in 6% (n=23) of degarelix treated patients and 2% (n=4) of leuprolide treated patients, with none being considered serious or leading to withdrawal. One patient with a long history of hepatitis was withdrawn from the study due to increased hepatic enzymes of "moderate severity" possibly related to degarelix (enzyme levels not provided).

Bilirubin levels > ULN were observed in 8% (n=33) of degarelix treated patients and 11% (n=23) of leuprolide treated patients, and shifts from low/normal to high levels occurred in 5% and 7% of patients, respectively. No increases in total bilirubin were reported as AEs. Abnormally high SAP levels (defined as 3x ULN + 25% increase) were observed in 8% (n=34) of degarelix treated patients and 7% of leuprolide treated patients. Abnormally high gamma-GT levels (defined as > 3x ULN) were observed in 8% of degarelix treated patients and 7% of leuprolide treated patients. One patient in the D240/80 group with an elevated gamma-GT assessed as being clinically significant and possibly related to treatment was withdrawn from the study. In this patient, gamma-GT had been elevated prior to first dosing and no other hepatic enzymes were elevated.

In the *Phase II/III studies (1 month regimen)*, there were 2 patients treated with degarelix with ALT > 3x ULN + bilirubin > 2x ULN and 2 patients treated with degarelix with ALT > 3x ULN + bilirubin > 1.5-2x ULN. The sponsor considers that there are alternative reasons for these findings other than drug induced liver injury. The narratives of these patients have been reviewed and the sponsor's interpretation is considered to be reasonable as there were alternative plausible explanations for the results (2 patients - gallstones with associated clinical symptoms and/or signs; 1 patient - sodium alendronate [literature suggests that this is a rare but possible cause of hepatotoxicity] for osteoporosis appears to have been started prior to abnormalities; 1 patient - unlikely temporal relationship).

Cholesterol

In the *pivotal study [CS21]*, both degarelix and leuprolide were associated with an increase in the proportion of patients shifting from low/normal to high levels (58% and 63%, respectively). The mean increases from baseline were 0.247 and 0.335 mmol/L with degarelix and leuprolide, respectively. The percentage of patients with markedly abnormal levels (≥ 8.0 mmol/L) were 10% for degarelix treated patients and 6% for leuprolide treated patients. There were no biochemical data on other serum lipids. Hypercholesterolaemia was reported as an AE in 5% (n=19) and 2% (n=5) of degarelix and leuprolide treated patients, respectively. AEs of hyperlipidaemia, dyslipidaemia, and hypertriglyceridaemia were reported in < 1% of degarelix and leuprolide treated patients with the total number of patients for these three AEs being 5 and 3, respectively.

Glucose

There were no data on blood glucose levels or glycosylated haemoglobin concentrations in patients with prostate cancer. Testing for these parameters was not specified in the pivotal study [CS12] protocol. Increased blood glucose was described as an AE in < 1% (n=1) of degarelix treated patients and 0% of leuprolide treated patients. Diabetes mellitus was reported as an AE in 2% (n=7) of degarelix treated patients and 1% (n=3) of leuprolide treated patients, with 1 case in each treatment group being considered to be an SAE.

Urinalysis

Urinalysis results in the pivotal study [CS21] were similar for degarelix and leuprolide treated patients with the most common abnormality being haematuria; 2% [n=8] and 1%

[n=8], respectively. Glycosuria occurred in 1 patient treated with degarelix and 0 patients treated with leuprolide.

Vital Signs

Systolic blood pressure (SBP), diastolic blood pressure (DBP, pulse rate (PR): In the *pivotal study [CS21]*, there was a mean reduction in SBP of about 3 mmHg from a baseline of 135 mmHg after degarelix (n=409) and about 2 mmHg from a baseline of 135 mmHg after leuprolide (n=201). The respective reductions in DBP were about 1.3 mmHg from a baseline of 78 mmHg and about 1 mmHg from a baseline of 78 mmHg. Markedly abnormal increases in SBP (≥ 180 + ≥ 20 from baseline) occurred in 9% of degarelix treated patients and 11% of leuprolide treated patients, while markedly abnormal increases in DBP (≥ 105 + ≥ 15 from baseline) occurred in 4% of patients in both treatment groups. Markedly abnormal reductions in SBP (≤ 90 and decrease of ≥ 20) and DBP (≤ 50 and decrease of ≥ 15) occurred in 5% of degarelix treated patients and 3% to 5% of leuprolide treated patients. Hypertension was reported as an AE in 6% (n=26) and 4% (n=8) of degarelix and leuprolide treated patients, respectively. Hypotension and orthostatic hypotension were reported in < 1% of patients in both treatment groups. Changes in pulse rate were small and not significant.

Weight: Markedly abnormal increases in weight (≥ 7% from b aseline) occurred in 10% of degarelix treated patients and 13% of leuprolide treated patients. The respective results for markedly abnormal decreases in weight (≥ 7% from baseline) were 3% and 5%. Weight increase was reported as an AE in 10% of degarelix treated patients and 12% of leuprolide treated patients.

Electrocardiogram (ECG): Cardiac repolarisation has been shown to be slower and longer in castrated men than in men with normal testosterone levels. In the *pivotal study [CS21]*, 20% (n=81) of degarelix treated patients had QT intervals (corrected for rate [QTc interval] using Fridericia's correction [QTcF]) ≥ 450 msec at the end of the study compared with 19% (n=40) of leuprolide treated patients. Markedly abnormal QTcF intervals (≥ 500 msec) occurred in 0.7% (n=3) of degarelix treated patient and 2% (n=4) of leuprolide treated patients. There were no reports of syncope, torsades de pointes, ventricular fibrillation or sudden death in degarelix treated patients with QTcF ≥ 500 msec. One leuprolide treated patient with a QTcF ≥ 500 msec and a previous history of syncope experienced syncope and cardiac arrhythmia 20 days after a measurement of 503 msec, but continued in the study. The mean increase from baseline in QTcF at study end was 12.3 msec (3.0% increase from baseline 405 msec) in degarelix treated patients and 14.3 msec (3.5% increase from baseline of 404 msec) in leuprolide treated patients. Increases from baseline of ≥ 60 msec were observed in 3% (n=13) of degarelix treated patients and 7% (n=15) of leuprolide treated patients. QTcF results for both degarelix dosing regimens showed no dose response relationship and differences between treatments were small. There were only small increases in QTcF on Day 3 (that is, day of t_{max} for degarelix after 240 mg) of 2.4 msec for degarelix and 0.8 msec for leuprolide. The increase in QTcF at study endpoint was greater than at Day 3 for both degarelix and leuprolide.

Sub-Groups

Age: In the Phase II/III studies (1 month regimen), 18% of patients were aged < 65 years, 40% aged 65 to < 75, and 42% aged ≥ 75 years. The incidence of degarelix related AEs was lower in the younger age group than in the two older age groups (76%, 84%, 88%, respectively). The differences appear to mainly be due to lower incidences of hypertension and weight gain in younger patients and a higher incidence of increased ALT in the older patients.

Race: In the Phase II/III studies (1 month regimens) the majority of patients were Caucasian (87%) with 5% being black and 8% being "other". It is considered that the imbalance between the racial groups precludes meaningful conclusions being made about AE differences.

Weight: There did not appear to be any clinically significant association between AEs and weight.

Clinical Summary and Conclusions

Efficacy

The submission has satisfactorily established the efficacy of the proposed degarelix dosage regimen for the proposed indication in one pivotal Phase III study [CS21]. The efficacy results from the pivotal study are supported by four Phase II studies [CS07, CS15, CS12, CS14]. These five studies were all open-label and only the pivotal study included a control group. The efficacy endpoints in the five studies were primarily biochemical (testosterone suppression) and none of the studies satisfactorily assessed overt clinical endpoints. However, testosterone suppression to castration levels is a well established surrogate efficacy endpoint for drugs intended to be used for androgen deprivation therapy in patients with prostate cancer. The efficacy conclusions relating to the proposed treatment regimen (D240/80) from pivotal study [CS21] are summarised below. There are no satisfactory efficacy data beyond 12 months.

The pivotal study showed that in patients treated with D240/80 the Kaplan-Meier estimate of the probability of testosterone suppression (≤ 0.5 ng/mL) from Day 28 to Day 364 was 97.2 % [95% CI: 93.5, 98.9] in the ITT population. The lower limit of the 95% CI was 93.5% and was greater than the 90% limit specified as the efficacy criterion by the FDA. In addition, the mean difference in the probabilities between D240/80 and L7.5 was 0.9% [97.5% CI: -3.2, 5.0], with the lower limit of the 97.5% CI of -3.2% being greater than the pre-specified non-inferiority limit of -10% (that is, D240/80 is non-inferior to L7.5). The two degarelix treatment regimens are considered to be clinically equivalent, although no formal statistical comparison of the two regimens was undertaken.

Testosterone levels were rapidly suppressed after initiation of treatment with degarelix 240 mg with ≥ 95% of patients being suppressed to levels ≤ 0.5 mg/mL at Day 3 compared with 0% of L7.5 mg treated patients. In contrast, there was a surge in testosterone levels in the first 2 weeks after treatment with L7.5 in 80.1% of patients compared with ≤ 0.5% of patients given degarelix 240 mg. Sufficient testosterone response from Day 28 to Day 364 was observed in 97.8% of D240/80 treated patients and 96.9% of L7.5 treated patients. There was a rapid fall in LH levels after initiation of treatment with degarelix 240 mg with reduction to about 88% of median baseline levels at Day 1 with levels then remaining suppressed until Day 364 with both maintenance doses (80 mg and 160 mg). However, after an initial dose of L7.5, LH increased to > 400% median baseline levels at Day 1 and then fell to Day 56 after which time levels were maintained until Day 364. Similarly, FSH levels rapidly fell by Day 7 after degarelix 240 mg with the reduction being maintained to Day 364 with both maintenance doses (80 mg and 160 mg) compared with an initial surge on Day 1 after L7.5 followed by a fall to plateau levels from Day 56 to 364. PSA levels fell after initial doses of degarelix 240 mg and L7.5, with falls at Day 14 and 28 being greater with degarelix.

Safety

The submission has satisfactorily established the safety of degarelix for the proposed indication. Overall, the safety of D240/80 was similar to L7.5 mg. No unexpected AEs were seen with degarelix. The number of patients exposed to degarelix is considered to be

adequate as is the duration of exposure. The total number of patients exposed to degarelix was 1836. The "rule of three" suggests that this patient number is sufficient to be 95% confident that it will detect ADRs which occur with an incidence of 0.2% [Hanley and Lippman-Hand, 1983; Jovanovic and Levy, 1997].

In the pivotal study, 169 patients were treated with D240/80 for at least 12 months with the corresponding figure for D240/160 being 163. In the pivotal study, the safety profiles of the two degarelix treatment regimens were similar to that of leuprolide 7.5 mg. However, both degarelix regimens were associated with a greater incidence of injection site reactions than the leuprolide regimen due to differences in route of administration, and number and volume of injections. Injection site reactions were more common with D240/160 than with D240/80.

The hypersensitivity profile of degarelix was extensively investigated. No evidence emerged linking the drug to severe life threatening hypersensitivity reactions such as anaphylaxis, angioedema, or severe skin/mucosal reactions. The hypersensitivity profiles of D240/160, D240/80 and L7.5 are considered to be similar. In the pivotal study, anti-degarelix antibodies during the first year of treatment were detected in 14% of D240/160 treated patients and 10% of D240/80 treated patients. In patients in the total safety database treated for 2 years, 34% developed antibodies. The proportion of patients with antibodies increased with duration of exposure. No association was observed between hypersensitivity reactions and the presence of anti-degarelix antibodies. Efficacy was not impaired in patients with anti-degarelix antibodies.

In the pivotal study, SAEs and deaths occurred more commonly with leuprolide than with degarelix, 11% (n=45) vs 14% (n=28), and 2.4% (n=10) vs 4.5% (n=9), respectively. The SAEs and causes of death were typical of an elderly population with prostate cancer. Increased liver ALT and AST levels occurred commonly with both degarelix and leuprolide, while increased total bilirubin levels occurred less commonly. However, the observed elevated liver ALT, AST and bilirubin levels were not associated with clinical liver disease. The pivotal study excluded patients with hepatic or symptomatic biliary disease or with ALT or bilirubin levels > ULN.

In the pivotal study, incidence rates for cardiovascular AEs (apart from stroke) were lower in degarelix treated patients than in leuprolide treated patients. In addition, incidence rates for cardiovascular AEs (apart from heart failure) were lower in degarelix treated patients than background rates in patients with prostate cancer treated with GnRH therapy (SEER cohort). Serum cholesterol shifted from low/normal to high levels in the majority of degarelix and leuprolide treated patients (58% vs 63% respectively) with markedly abnormal levels (≥ 8.0 mmol/L) occurring in 10% and 6% of patients, respectively. No biochemical data were collected on other lipids in patients with prostate cancer. There were no data on changes in blood glucose levels after degarelix or leuprolide in the pivotal study. However, data from this study showed that AEs of hyperglycaemia and diabetes mellitus were uncommon. The incidences of other AEs associated with androgen deprivation therapy were similar for degarelix and leuprolide (ie weight gain, hot flushes, QTc prolongation, reduction in Hb). There were no data in the submission on changes in bone density, but it can be anticipated that decreases in bone density will occur after prolonged treatment with degarelix due to its ability to suppress serum testosterone to castration levels.

The sponsor's decision not to collect data on serum glucose and serum lipids other than cholesterol are unusual given that androgen deprivation therapy is associated with increased glucose and insulin levels suggesting decreased insulin sensitivity and an increased incidence of cardiovascular disease. In response to questions about the failure to collect data on these biochemical parameters the sponsor argues that the available AE data relating to these

parameters (for example, hyperglycaemia, diabetes mellitus, cardiovascular disease) from pivotal study CS21 suggests no apparent differences between degarelix and leuprolide. Furthermore, the sponsor argues that changes in serum glucose and lipids can be anticipated as they are metabolic effects resulting from androgen deprivation. While there is substance to the sponsor's arguments, the failure to at least measure serum glucose level in the pivotal study is unusual and suggests an inadvertent oversight. However, the failure to measure serum glucose and serum lipids other than cholesterol should not preclude registration.

Recommendation

The evaluator recommended approval of degarelix for the treatment of prostate cancer in patients in whom androgen deprivation therapy is warranted.

Approval of the proposed degarelix treatment regimen was also recommended (that is, a starting dose of 240 mg administered as two SC injections (2 x 3 mL injection [40 mg/ml]) followed 28 days later by a maintenance dose of 80 mg administered as one SC injection (1x 4 mL injection [20 mg/mL]) to be then administered every 28 days).

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There were no objections to registration on chemistry, manufacturing or quality control grounds.

Nonclinical

There were no preclinical objections to registration. The observed toxicities of degarelix were generally consistent with the known mechanism of action of the drug (for example, atrophy of male reproductive organs). The only concern raised related to the occurrence of severe local injection site reactions. Injection site reactions were also a common adverse event in the pivotal clinical study (see below).

Clinical

The clinical evaluator has recommended approval of the application.

Pharmacokinetics (PK)

The evaluator commented that the PK of degarelix were highly variable, both in healthy volunteers and in patients. The PK also varied with the concentration of the suspension used in the studies. After the same subcutaneous (SC) dose, systemic exposure was greater with low concentration suspensions compared to high concentration suspensions. Note that the application seeks approval for two different concentrations of suspension – 40 mg/mL and 20 mg/mL.

SC administration resulted in an initial rapid release of degarelix into the systemic circulation followed by a prolonged slow release phase. Absolute bioavailability following SC administration was estimated at approximately 32 – 39%. However, this estimate was derived from study CS05, which used a dilute suspension of degarelix (5 mg/mL), and a parallel group design. Following IV administration to elderly males, volume of distribution (V_{ss}) was 0.65 – 0.82 L/kg (p 53). Protein binding was 90%. Following IV administration to healthy

males, the proportion of degarelix excreted unchanged in the urine was 18.5%, indicating predominantly metabolic clearance. In vitro data indicated that the drug is not a substrate for the CYP450 system. Metabolism is considered to occur through proteolytic degradation, with excretion of cleavage products via the hepato-biliary system.

Following IV administration, the clearance of degarelix in elderly males was 35 – 47 mL/kg/hr and half-life was between 13.6 and 23.7 hours. Following SC injection of the depot formulations half-life was 41 – 53 days.

The submission included a PK study conducted in subjects with mild or moderate hepatic impairment. Systemic exposure was not increased. The effect of severe impairment has not been studied. No study has been conducted in patients with renal impairment. However, the PK data suggest that renal clearance is a minor route of elimination.

In vitro data suggested that the drug does not have potential for PK drug interactions.

Efficacy

The submission included a number of Phase II studies aimed at determining the appropriate dose, based on the reduction of testosterone to castrate levels (<0.5 ng/mL).

The main evidence for efficacy comes from one open, randomised controlled trial (*Study CS21*)**.** The study included subjects with *any* stage of disease in whom androgen deprivation was indicated (but did not allow neoadjuvant use). This included patients with a rising PSA after prostatectomy or radiotherapy with curative intent. Subjects were randomised to one of three treatment arms:

- Degarelix 240 mg (40 mg/mL) initially then 80 mg (20 mg/mL) every 28 days;
- Degarelix 240 mg (40 mg/mL) initially then 160 mg (40 mg/mL) every 28 days;
- Leuprorelin 7.5 mg every 28 days.

Treatment was continued for 12 months. The dosage regimen for leuprorelin is identical to that registered for Lucrin and Eligard in Australia.

The primary efficacy parameter was testosterone reaching castration levels (< 0.5 ng/mL). This parameter has previously been accepted by the Australian Drug Evaluation Committee (ADEC) and the TGA as a valid surrogate efficacy measure for GnRH agonists in the treatment of prostate cancer. The primary endpoint was the cumulative probability of testosterone being < 0.5 ng/mL between Day 28 and Day 364. Non-inferiority with leuprorelin was to be concluded if the lower 97.5% CI for the difference between degarelix and leuprorelin on this endpoint was > -10%. The cumulative probability was 97.2% in the degarelix 240/80 group and 96.4% in the leuprorelin group. The lower 97.5% CI for the difference was -3.2% and non-inferiority was therefore concluded. The results for the degarelix 240/160 group did not suggest improved efficacy with the higher maintenance dose.

Degarelix treatment was not associated with an early surge of testosterone, LH or FSH, whereas this was observed with leuprorelin. Reductions in PSA occurred in all three treatment groups.

Safety

In the phase II and III studies included in the submission, a total of 1,836 patients were exposed to degarelix. Of these, a total of 1334 patients were exposed for ³ 6 months and 1148 for ³ 12 months.

The most informative safety data come from the pivotal study, which allowed comparison of the safety profile of degarelix with that of leuprorelin. Degarelix was associated with an increased incidence of:

- Injection site reactions (40% vs < 1%) - pain, erythema, swelling etc. The majority of these were mild or moderate in severity
- Chills (4% vs 0 %); and
- Influenza-like symptoms (2% vs 0 %).

It appeared to be associated with a lower incidence of arthralgia (4% vs 9%) and erectile dysfunction (1% vs 4%). The incidence of hot flushes was comparable.

There was no excess of grade III/IV adverse events, serious adverse events, withdrawals due to adverse events or deaths. There was no notable differences between the two treatment groups with respect to laboratory parameters or ECG findings.

Risk-Benefit Analysis

The pivotal study has demonstrated that degarelix at the proposed dosage regimen is non-inferior to leuprorelin with respect to efficacy. It is associated with an increased incidence of injection site reactions most of which were mild or moderate in severity. The increased incidence of injection site reactions did not result in an increased incidence of withdrawal from treatment due to adverse events. The drug has the potential safety advantage of not being associated with the initial testosterone surge associated with GnRH agonists. Overall the Delegate believed it is reasonable to conclude that the risk-benefit profile of degarelix is comparable to that of leuprorelin and he proposed to approve the application.

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal and recommended approval for the indication:

Treatment of patients with prostate cancer in whom androgen deprivation therapy is warranted.

In making this recommendation, the ACPM agreed with the Delegate that efficacy has been satisfactorily shown. The sponsor had also demonstrated that degarelix at the proposed dosage regimen is non-inferior to leuprorelin. The Committee further noted that it is associated with an increased incidence of injection site reactions most of which were mild or moderate in severity. However, the increased incidence of injection site reactions did not result in an increased incidence of withdrawal from treatment due to adverse events. Although the Committee queried the lack of data on long-term (>12 months) duration of action, the drug has the potential safety advantage of not being associated with the initial testosterone surge associated with GnRH agonists and therefore the risk-benefit profile of degarelix was considered acceptable.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Firmagon powder and solvent for injection vial containing degarelix 80mg and 120mg for:

Treatment of patients with prostate cancer in whom androgen deprivation therapy is warranted.

Attachment 1. Product Information

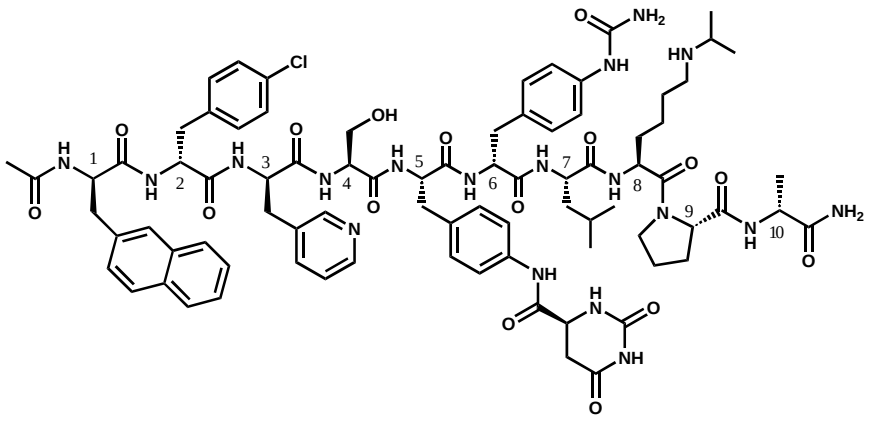
FIRMAGON® degarelix (as acetate)

FIRMAGON 120 mg, powder and solvent for injection, depot
FIRMAGON 80 mg, powder and solvent for injection, depot

NAME OF THE MEDICINE

Degarelix (as acetate). Degarelix is a third generation gonadotrophin releasing hormone (GnRH) antagonist (blocker). It is a synthetic decapeptide, which forms a depot following subcutaneous injection; this depot formation results in a sustained release of degarelix.

The structural formula of degarelix is



It has an empirical formula of $C_{82}H_{103}N_{18}O_{16}Cl$ and a monoisotopic mass of 1630.75 Da. CAS Number: 214766-78-6.

DESCRIPTION

FIRMAGON is a sterile, off-white powder plus a clear, colourless solvent for reconstitution. The sterile powder is a freeze-dried product containing degarelix (as the acetate) and mannitol. The solvent consists of sterile water for injections. FIRMAGON delivers degarelix acetate, equivalent to 120 mg of degarelix for the starting dose, and 80 mg of degarelix for the maintenance dose. The 80 mg vial contains 200 mg mannitol and the 120 mg vial contains 150 mg mannitol.

Degarelix has a natural propensity to gel in aqueous media by its inherent physicochemical characteristics. At concentrations above ca. 1 mg/mL, aqueous degarelix aggregates and cross-links in a gel-forming network, resulting in the formation of a hydrogel. While the process does not take place visibly in the reconstituted product, the depot formation happens instantaneously following subcutaneous administration.

PHARMACOLOGY

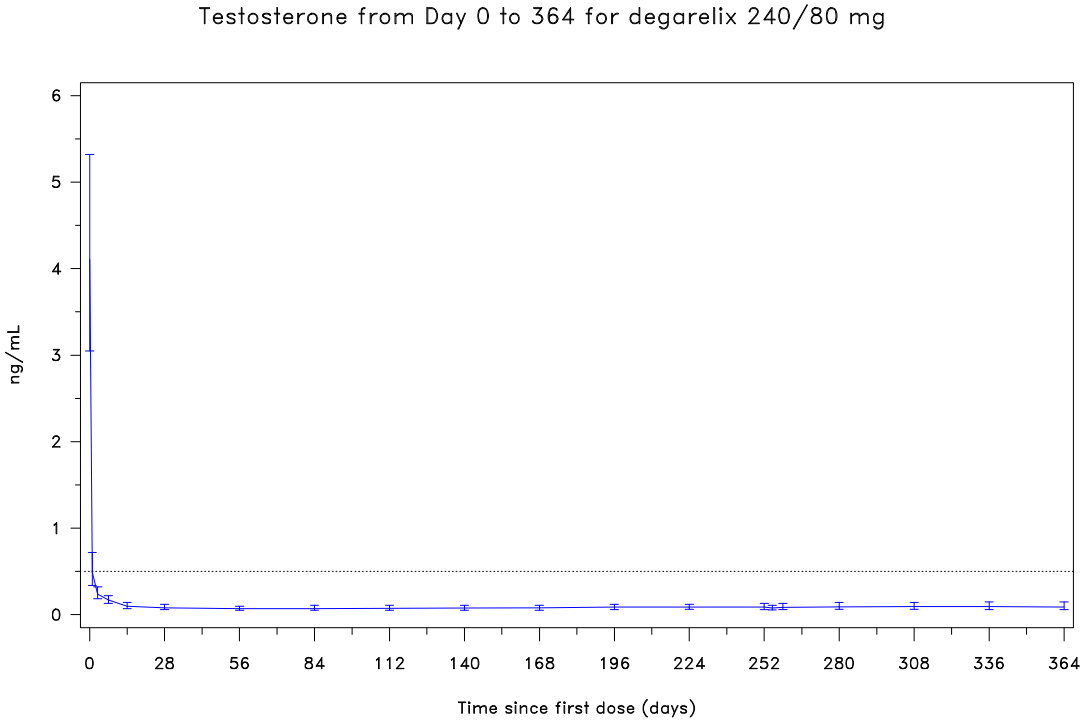
Pharmacodynamics

Degarelix is a selective GnRH receptor antagonist (blocker) that competitively and reversibly binds to the pituitary GnRH receptors with nanomolar potency, thereby rapidly reducing the release of gonadotrophins and consequently testosterone (T). Prostate cancer is sensitive to testosterone deprivation, a mainstay principle in the treatment of hormone-sensitive prostate cancer. Unlike GnRH agonists, GnRH receptor blockers do not induce a luteinising hormone (LH) surge with subsequent testosterone surge/tumour stimulation and potential symptomatic flare after the initiation of treatment.

A single dose of 240 mg FIRMAGON, followed by a monthly maintenance dose of 80 mg, rapidly causes a decrease in the concentrations of LH, follicle stimulating hormone (FSH) and subsequently testosterone. The plasma concentration of dihydrotestosterone (DHT) decreases in a similar manner to testosterone.

FIRMAGON is effective in achieving and maintaining testosterone suppression well below medical castration level of 0.5 ng/mL. Maintenance monthly dosing of 80 mg resulted in sustained testosterone suppression in 97% of patients for at least one year. Median testosterone levels after one year of treatment were 0.087 ng/mL [interquartile range 0.06-0.15] N=167.

Figure 1: Plasma testosterone levels from day 0 to 364 for degarelix 240 mg/80 mg (median with interquartile ranges)



Pharmacokinetics

Absorption

FIRMAGON forms a depot upon subcutaneous administration, from which degarelix is released to the circulation. The relevant pharmacokinetic results of FIRMAGON evaluated in prostate cancer patients are summarised in Table 1. Median degarelix trough concentrations in the maintenance phase with 80 mg at a concentration of 20 mg/mL was 10.9 ng/mL.

Table 1: Pharmacokinetic parameters after subcutaneous administration of FIRMAGON 240 mg at a concentration of 40 mg/mL (single dose). Median (5-95 percentiles), *observed values day 0-28, **model estimated values.

Pharmacokinetic parameter	FIRMAGON 240 mg
C_{max} (ng/mL)*	53.4 (27.3-126.5)
T_{max} (days)**	1.4 (1.1-2.0)
$T_{1/2}$ (days)**	43 (27-73)
$AUC_{0-\infty}$ (day·ng/mL)**	1240 (733-2140)

Following subcutaneous administration of 240 mg FIRMAGON at a concentration of 40 mg/mL to prostate cancer patients, degarelix reaches a maximal concentration after 1-2 days and decreases thereafter in a biphasic fashion, with a median terminal half-life of approximately 43 days. The long half-life after subcutaneous administration is a consequence of a very slow release of degarelix from the FIRMAGON depot formed at the injection site(s). The pharmacokinetic behaviour of the drug is influenced by its concentration in the injection. The estimated values for bioavailability from population pharmacokinetic modelling were approximately 60% and 40% for dose concentrations 20 mg/mL and 40 mg/mL respectively.

Distribution
The distribution volume at steady state in healthy elderly men (≥65 years) was in the range of 0.65-0.82 L/kg. Plasma protein binding is estimated to be approximately 90%.

Metabolism
Degarelix is subject to common peptidic degradation during the passage of the hepato-biliary system and is mainly excreted as peptide fragments in the faeces. No significant metabolites were detected in plasma samples after subcutaneous administration. In vitro studies have shown that degarelix is not a substrate for the human CYP450 system.

Excretion
In healthy men, approximately 20-30% of a given dose of degarelix was renally excreted, suggesting that approximately 70-80% is excreted via the hepato-biliary system in humans. The clearance in healthy elderly men is 35-50 mL/h/kg. After i.v. administration terminal half-life was 10-16 hours which is much shorter than for s.c. administration, indicating that the observed terminal phase after s.c. administration is determined by the absorption rate rather than the elimination rate.

CLINICAL TRIALS
The efficacy and safety of FIRMAGON was evaluated in an open-label, multi-centre, randomised, active comparator, parallel-group study. The study investigated the efficacy and safety of FIRMAGON one month dosing regimens; a starting dose of 240 mg (40 mg/mL) followed by monthly doses of 160 mg (40 mg/mL) or 80 mg (20 mg/mL) s.c., in comparison to leuprorelin 7.5 mg i.m. in patients with prostate cancer requiring androgen deprivation therapy. In total 620 patients were randomised to one of the three treatment groups.

Of the patients randomised
- 31% had localised prostate cancer
- 29% had locally advanced prostate cancer
- 20% had metastatic prostate cancer
- 7% had an unknown metastatic status
- 13% had previous curative intent surgery or radiation and a rising PSA

Baseline demographics were similar between the arms. The primary objective was to demonstrate that FIRMAGON is effective with respect to achieving and maintaining testosterone suppression to below 0.5 ng/mL, during 12 months treatment. In total 504 (81%) patients completed the study. In the degarelix treatment group 240/80 mg, 41 (20%) patients and in the leuprorelin treatment group, 32 (16%) patients discontinued the study.

The primary efficacy endpoint of the study was the cumulative probability of testosterone ≤ 0.5 ng/mL from Day 28 through Day 364.

For each of the three treatment groups, the cumulative one-year testosterone suppression probabilities were estimated using the Kaplan Meier method applied to time to testosterone >0.5 ng/mL from Day 28 to Day 364. Associated 95% confidence intervals (CI) were calculated using the log-log transformation of survivor function, Greenwood's formula and the delta-method. Differences in one-year testosterone suppression rates between the degarelix treatment groups and leuprorelin 7.5 mg were assessed using a 97.5% CI (i.e. multiplicity adjusted) calculated by normal approximation using the pooled standard error.

To assess the efficacy of degarelix, two hypotheses were tested:

One criterion was to determine whether the one–year cumulative suppression rate was statistically significantly larger than 90%, that is, whether the lower bound of the 95% confidence interval (CI) for the cumulative probability of testosterone ≤0.5 ng/mL from Day 28 to Day 364 was not lower than 90%. The second criterion was to determine whether degarelix was non-inferior to leuprorelin 7.5 mg with respect to the cumulative probability of testosterone ≤0.5 ng/mL from Day 28 to Day 364. The non-

inferiority limit for the difference between treatments (degarelix versus leuprorelin 7.5 mg) was -10 percentage points.

The trial was powered, assuming true cumulative suppression rates of 96% and 15 % annual drop out rate, for each treatment arm, to meet, with >90% probability (power), each of the efficacy criteria. Power calculations were based on simulation experiments and the above mentioned analysis methods.

The results are presented in Tables 2-a and 2-b and in Figure 2.

Table 2-a: Primary endpoint (first criterion): Kaplan-Meier estimates of the cumulative probability of testosterone ≤0.5 ng/mL from day 28 to day 364 – ITT analysis set

	Degarelix 240/160 mg (N=202)			FIRMAGON 240/80 mg (N=207)			Leuprorelin 7.5 mg (N=201)		
	T>0.5 ng/mL	Cens	(%)	T>0.5 ng/mL	Cens	(%)	T>0.5 ng/mL	Cens	(%)
Day 28 → 364	3	199	(98.3%)	5	202	(97.2%)	7	194	(96.4%)
95% CI			[94.8;99.4%]			[93.5;98.8%]			[92.5;98.2%]

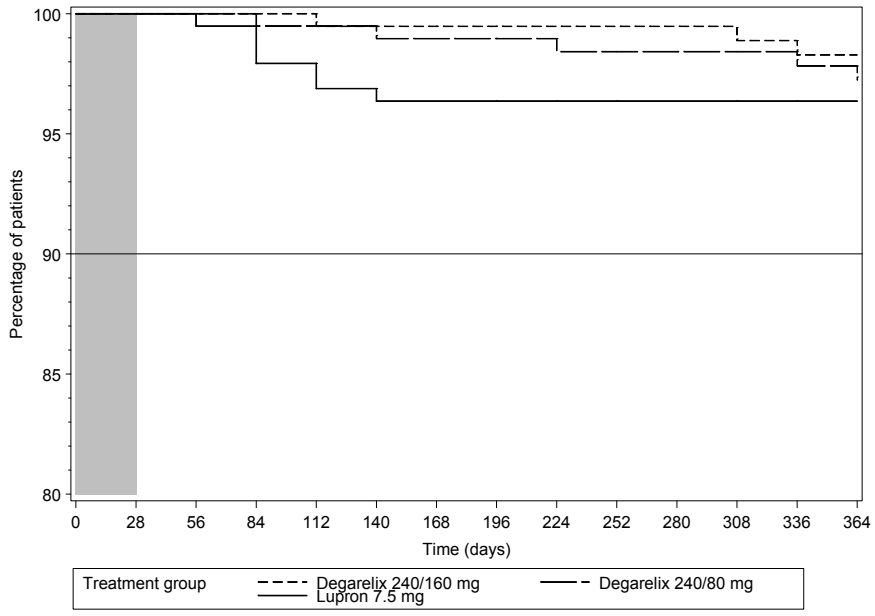
T>0.5 ng/mL = Cumulative number of patients with testosterone >0.5 ng/mL
Cens = Number of censored observations before or at Day 364
(%) = Estimated probability of all testosterone values ≤0.5 ng/mL

Table 2-b: Primary endpoint (second criterion): Difference in Kaplan-Meier estimates of the cumulative probability of testosterone ≤0.5 ng/mL from day 28 to day 364 between degarelix and leuprorelin arms – ITT analysis set

Degarelix 240/160 mg (N=202)		FIRMAGON 240/80 mg (N=207)	
Estimate (%)	97.5% CI (%)	Estimate (%)	97.5% CI (%)
1.9%	[-1.8;5.7%]	0.9%	[-3.2;5.0%]

Note: the non-inferiority margin for the difference to leuprorelin 7.5 mg is -10 percentage points, the Lower Limit of the 97.5% CI is to be larger than -10 percent points to claim non-inferiority to leuprorelin

Figure 2: Kaplan-Meier plot of the cumulative probability of testosterone ≤0.5 ng/mL from day 28 and onwards – ITT analysis set



Tables 2-a and 2-b indicate that the primary endpoint according to both criteria has been met. Both degarelix arms have statistically significantly demonstrated a response larger than 90% and have proven to be non-inferior to leuprorelin. Figure 2 depicts, by means of a Kaplan-Meier plot, the cumulative probability of T ≤0.5 ng/mL as a function of time for each treatment arm.

Similar results were obtained for the per-protocol analysis set.

In addition the study included a range of secondary endpoints relating to testosterone suppression and PSA levels.

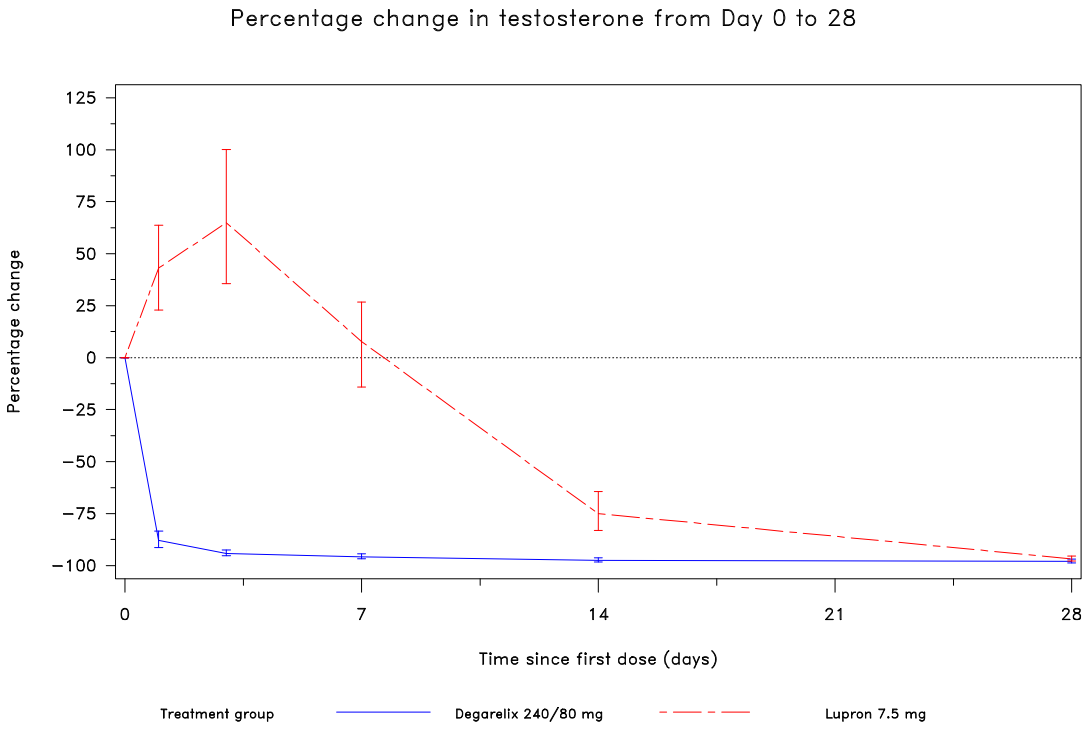
Attainment of serum Testosterone (T) ≤0.5 ng/mL:
FIRMAGON is effective in achieving fast testosterone suppression, see Table 3

Table 3: Percentage of patients attaining T≤0.5 ng/mL after start of treatment

Time	FIRMAGON 240/80 mg s.c.	Leuprorelin 7.5 mg i.m.
Day 1	52%	0%
Day 3	96%	0%
Day 7	99%	1%
Day 14	100%	18%
Day 28	100%	100%

Avoidance of testosterone surge:
None of the FIRMAGON treated patients experienced a testosterone surge; there was an average decrease of 94% in testosterone at day 3. Most of the leuprorelin treated patients experienced testosterone surge; there was an average increase of 65% in testosterone at day 3. Surge was defined as testosterone exceeding baseline by ≥15% within the first 2 weeks. This difference was statistically significant (p<0.001).

Serum levels of testosterone over time:
Figure 3: Percentage change in testosterone from baseline by treatment group until day 28 (median with interquartile ranges)

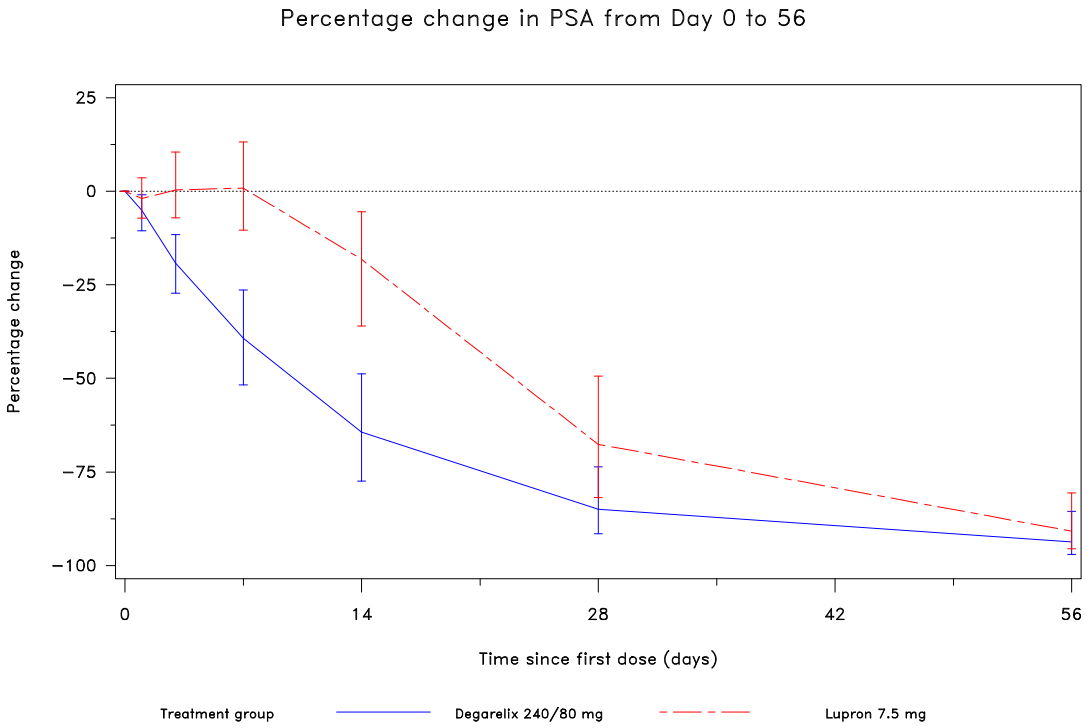


Attainment of prostate specific antigen (PSA) reduction:
Tumour size was not measured directly during the clinical trial programme, but there was an indirect beneficial tumour response as shown by a 95% reduction after 12 months in median PSA for FIRMAGON.

The median PSA in the study at baseline was:

- for the FIRMAGON treatment group 19.8 ng/mL (interquartile range: P25 9.4 ng/mL, P75 46.4 ng/mL)
- for the leuprorelin 7.5 mg treatment group 17.4 ng/mL (interquartile range: P25 8.4 ng/mL, P75 56.5 ng/mL)

Figure 4: Percentage change in PSA from baseline by treatment group until day 56 (median with interquartile ranges)



This difference was statistically significant ($p<0.001$) at the pre-specified analysis at day 14 and day 28.

Prostate specific antigen (PSA) levels are lowered by 64% two weeks after administration of FIRMAGON, 85% after one month, 95% after three months, and remained suppressed (approximately 97%) throughout the one year of treatment. From day 56 to day 364 there were no significant differences between FIRMAGON and the comparator in the percentage change from baseline.

Change in ECGs:
In the confirmatory study comparing FIRMAGON to leuprorelin periodic electrocardiograms were performed. Both therapies showed QT/QTc intervals exceeding 450 msec in approximately 20% of the patients. From baseline to end of study the median change for FIRMAGON was 12.3 msec (3.2%) and for leuprorelin was 16.7 msec (3.5%).

Anti-degarelix antibody development has been observed in 10% of patients after treatment with FIRMAGON for 1 year. There is no indication that the efficacy or safety of FIRMAGON treatment is affected by antibody formation.

INDICATIONS
FIRMAGON is a GnRH receptor blocker indicated for treatment of patients with prostate cancer in whom androgen deprivation is warranted.

CONTRAINDICATIONS
Hypersensitivity to degarelix or any other GnRH antagonists, or to any of the product excipients.
FIRMAGON is not indicated in women or paediatric patients.

PRECAUTIONS

Effect on QT/QTc interval

Long-term androgen deprivation therapy may prolong the QT interval (See PHARMACOLOGY). In the confirmatory study comparing FIRMAGON to leuprorelin periodic (monthly) ECGs were performed; changes in ECG measurements seen during one year of treatment were in the same range for degarelix and a GnRH-agonist (leuprorelin) used as comparator. Both therapies showed QT/QTc intervals exceeding 450 msec in approximately 20% of the patients. Three (<1%) out of 409 patients in the degarelix group and four (2%) out of 201 patients in the leuprorelin 7.5 mg group, had a QTcF ≥ 500 msec. From baseline to end of study the median change in QTcF for degarelix was 12.0 msec and for leuprorelin was 16.7 msec.

FIRMAGON has not been studied in patients with a history of a corrected QT interval over 450 msec, in patients with a history of or risk factors for torsades de pointes and in patients receiving concomitant medicinal products that might prolong the QT interval (e.g. Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic medications). Therefore in such patients, the benefit/risk ratio of FIRMAGON must be thoroughly appraised.

Hypersensitivity

Patients in the degarelix program were carefully monitored post-injection for at least one hour at all dosing visits in order to detect any untoward effects that may be histamine mediated. Consequently, more than 1,700 patients at more than 19,000 dosing occasions have been observed. No cases of anaphylaxis, angioedema, or severe cutaneous skin reactions related to degarelix treatment have been observed.

Changes in bone density

Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with a GnRH agonist. It can be anticipated that long periods of testosterone suppression in men will have effects on bone density.

Antibody formation

Anti-degarelix antibody development has been observed in 10% of patients after treatment with FIRMAGON for one year. The prevalence of anti-degarelix antibodies increased with time. There is no indication that the efficacy or safety of FIRMAGON treatment is affected by antibody formation.

Changes in hepatic enzyme measurements

Patients with known or suspected hepatic disorder have not been included in long-term clinical trials with degarelix. Mild, transient increases in ALT and AST have been seen, these were not accompanied by a rise in bilirubin or clinical symptoms. Changes in laboratory values seen during one year of treatment were in the same range for degarelix and the GnRH-agonist (leuprorelin) used as comparator. Markedly abnormal (>3*ULN) liver transaminase values (ALT, AST and GGT) were seen in 2-6% of patients with normal values prior to treatment, following treatment with both medicinal products.

Route of administration

FIRMAGON is for subcutaneous administration only and is not to be administered intravenously.

Second line use

There are no data available on use of FIRMAGON in patients in whom treatment with GnRH agonists (e.g. leuprorelin, goserelin) has failed. FIRMAGON should only be used as first line androgen deprivation therapy.

Effects on fertility

Animal reproduction studies showed that degarelix caused infertility in male and female animals. This is due to the pharmacological effect; and the effect was reversible.

Use in Pregnancy (Category D)
FIRMAGON must not be used in pregnant women (see CONTRAINDICATIONS). Potential embryofetal effects were assessed with subcutaneous doses of degarelix during the period of organogenesis in rats at up to 0.09 mg/kg/day and in rabbits at up to 0.006 mg/kg/day, approximately 10% and 2% of the clinical dose on a mg/m^2 basis. An increase in the number of abortions, early embryofetal deaths and premature deliveries along with prolonged parturition were observed in both studies.

Genotoxicity
Degarelix did not cause genetic damage in standard *in vitro* assays (bacterial mutation, human lymphocyte chromosome aberration) nor in *in vivo* rodent bone marrow micronucleus tests.

Carcinogenicity
Two rodent carcinogenicity studies were performed with degarelix using maximum s.c doses of 50 mg/kg/2 weeks in mice and 25 mg/kg/2 weeks in rats, resulting in at least 7-fold the clinical AUC. No neoplastic changes were observed in male animals in either of these studies. An increase in hepatocellular adenomas was observed in female mice at all doses of degarelix tested, most likely as a result of reduced oestrogen. The incidence of haemangiosarcoma in the mesenteric lymph node of the female rats was increased at 25 mg/kg/2 weeks.

Patients with renal impairment
No pharmacokinetic studies in renally impaired patients have been conducted. Only about 20-30% of a given dose of degarelix is excreted unchanged by the kidneys. A population pharmacokinetics analysis of the data from the confirmatory Phase 3 study has demonstrated that the clearance of degarelix in patients with moderate renal impairment is reduced by 23%; therefore dose adjustment in patients with mild or moderate renal impairment is not recommended. Data on patients with severe renal impairment is scarce and caution is therefore warranted in this patient category.

Patients with hepatic impairment
Degarelix has been studied in a pharmacokinetic study in patients with mild to moderate hepatic impairment. No signs of increased exposure in the hepatically impaired were observed compared to healthy subjects. No shifts in liver function tests were observed 24 hours post-dose compared to baseline in patients with hepatic impairment. Dose adjustment is not necessary in patients with mild or moderate hepatic impairment. Patients with severe hepatic dysfunction have not been studied and caution is therefore warranted in this group.

Elderly
The patient population tested in the clinical program was typical of the intended target population of patients with prostate cancer. The mean age was 74 years (range 47 to 98 years). Population pharmacokinetic analysis shows only small changes in the clearance of degarelix related to age and weight. Therefore, dose adjustment is not warranted.

Interaction with Other Medicines
No drug-drug interaction studies have been performed.

Degarelix is not a substrate for the human CYP450 system and has been shown not to induce or inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5 to any great extent *in vitro*. Further, degarelix is not a substrate for p-glycoprotein or other human efflux/uptake transporters and is unlikely to interact with other medicines handled by transporters at clinically relevant concentrations. Therefore, clinically significant pharmacokinetic drug-drug interactions are unlikely.

Effects on ability to drive and use machines
No studies on the effects of FIRMAGON on the ability to drive and use machines have been performed.

ADVERSE EFFECTS
The most commonly observed adverse reactions during FIRMAGON therapy in the confirmatory Phase 3 study were due to the expected physiological effects of testosterone suppression, including hot

flushes and weight increase (reported in 25% and 7%, respectively, of patients receiving treatment for one year) and injection site adverse events.

The injection site adverse events reported were mainly pain and erythema, reported in 28% and 17% of patients, respectively, less frequently reported were swelling (6%), induration (4%) and nodule (3%). These events occurred primarily with the starting dose whereas during maintenance therapy the incidence of these events per 100 injections were: 3 for pain and <1 for erythema, swelling, nodule and induration. The reported events were mostly transient, of mild to moderate intensity and led to very few discontinuations (<1%).

The following adverse events were reported in 5% or more of patients in an active controlled trial comparing treatment with degarelix and leuprorelin, given as monthly administrations for 12 months, in patients with prostate cancer.

	FIRMAGON 240/80 mg (s.c.) N = 207	Leuprorelin 7.5 mg (i.m.) N = 201
	%	%
Percentage of subjects with adverse events	79	78
Body as a whole		
Injection site adverse events	35	<1
Weight increase	9	12
Fatigue	3	6
Chills	5	0
Cardiovascular system		
Hot flush	26	21
Hypertension	6	4
Musculoskeletal system		
Back pain	6	8
Arthralgia	5	9
Urogenital system		
Urinary tract infection	5	9
Digestive system		
Increases in transaminases and GGT	10	5
Constipation	5	5

The following adverse events were considered related to degarelix treatment by the investigator in the active controlled trial:
Very common ≥ 1/10: Hot flush, injection site reaction
Common ≥ 1/100 and < 1/10: Insomnia, dizziness, headache, nausea, constipation, liver transaminases increased, night sweats, chills, pyrexia, asthenia, fatigue, weight increased
Uncommon ≥ 1/1000 and < 1/100: Haemoglobin decreased, hypersensitivity, loss of libido, hypertension, diarrhoea, urticaria, hyperhidrosis, skin hyperpigmentation, erectile dysfunction, testicular atrophy, gynaecomastia, influenza-like illness.

Erectile dysfunction and loss of libido are common adverse events associated with androgen deprivation therapy.

Changes in laboratory parameters
Changes in laboratory values seen during one year of treatment were in the same range for degarelix and a GnRH-agonist (leuprorelin) used as comparator. Markedly abnormal (>3*ULN) liver transaminase values (ALT, AST and GGT) were seen in 2-6% of patients with normal values prior to treatment, following treatment with both medicinal products. Marked decrease in haematological values, haematocrit (≤0.37) and haemoglobin (≤115 g/L) were seen in 40% and 13-15%, respectively, of patients with normal values prior to treatment, following treatment with both medicinal products. It is unknown to what extent this decrease in haematological values was caused by the underlying prostate

cancer and to what extent it was a consequence of androgen deprivation therapy. Markedly abnormal values of potassium (≥5.8 mmol/L), creatinine (≥177 µmol/L) and BUN (≥10.7 mmol/L) in patients with normal values prior to treatment, were seen in 6%, 2% and 15% of degarelix treated patients and 3%, 2% and 14% of leuprorelin treated patients, respectively.

DOSAGE AND ADMINISTRATION

Dosage for Adult Males

Starting dose	Maintenance dose – monthly administration
240 mg administered as two s.c. injections of 120 mg at a concentration of 40 mg/mL	80 mg administered as one s.c. injection at a concentration of 20 mg/mL

The first maintenance dose should be given one month after the starting dose.

The therapeutic effect of FIRMAGON should be monitored by clinical parameters and by measuring PSA serum levels. Clinical studies have shown that testosterone (T) suppression occurs immediately after administration of the starting dose with 96% of the patients having plasma testosterone at medical castration levels (T≤0.5 ng/mL) after three days and 100% after one month. Long term treatment with the maintenance dose up to 1 year shows that 97% of the patients have sustained suppressed testosterone levels (T≤0.5 ng/mL).

In case the patient's clinical response appears to be sub-optimal, it should be confirmed that serum testosterone levels are remaining sufficiently suppressed. Since FIRMAGON does not induce a testosterone surge it is not necessary to add an anti-androgen as surge protection at initiation of therapy**.**

Administration
FIRMAGON is for subcutaneous administration only. IT MUST NOT BE ADMINISTERED INTRAVENOUSLY. Use in one patient on one occasion only. Contains no antimicrobial preservative.

FIRMAGON must be administered immediately after reconstitution. It is administered as a subcutaneous injection in the abdominal region. As with other drugs administered by subcutaneous injection, the injection site should vary periodically. Injections should be given in areas where the patient will not be exposed to pressure e.g. not close to waistband or belt and not close to the ribs. The injection site should not be rubbed or massaged as this might disperse the depot resulting in altered release.

Reconstitution
FIRMAGON is supplied as a powder to be reconstituted with water for injections. The reconstitution procedure needs to be carefully followed (see below and package insert). Administration of other concentrations is not recommended. The reconstituted product should be a clear liquid, free of undissolved matter.

Reconstitution of FIRMAGON single dose vials:

Presentation	Sterile Water for Injections	Total Product and Volume	Extractable Product and Volume	Final Concentration
120 mg	Add 3 mL	128 mg in 3.2 mL	120 mg in 3 mL	40 mg/mL
80 mg	Add 4.2 mL	88.2 mg in 4.4 mL	80 mg in 4 mL	20 mg/mL

1. Draw up the required volume of solvent (as specified in the table above) with the reconstitution needle. Discard the vial with the remaining solvent.
2. Inject the solvent gently into the powder vial. In order to keep the product and syringe sterile, DO NOT REMOVE THE SYRINGE AND THE NEEDLE.

3. KEEP THE VIAL IN AN UPRIGHT POSITION. Hold the vial (with the syringe in place) by the neck and swirl it very gently until the liquid looks clear and there is no powder or particulate matter visible. If the powder sticks to the sides of the vial above the liquid surface, slightly tilt the vial to dissolve the powder. AVOID SHAKING THE VIAL, in order to prevent foam forming. A ring of small air bubbles on the surface of the liquid is acceptable. The process may take up to 15 minutes but usually takes a few minutes.
4. Tilt the vial slightly and keep the needle at the bottom of the vial. Withdraw the required volume of solution (as specified in the table above) **without turning the vial upside down.**
5. Exchange the reconstitution needle with the administration needle for deep subcutaneous injection. Remove any air bubbles.
6. Grasp the skin of the abdomen, pinch the subcutaneous tissue. Prepare to perform a deep subcutaneous injection. To do so, insert the needle **deeply** at an angle of not less than **45 degrees**. DO NOT INJECT DIRECTLY INTO A VEIN. Before injecting, gently pull back the plunger to check if blood is aspirated. If blood appears in the syringe, the reconstituted product can no longer be used. Discontinue the procedure and discard the syringe and needle (reconstitute a new dose for the patient).
7. Inject the dose immediately after reconstitution.

Dose Adjustment in Specific Patient Populations
Elderly, Hepatically or Renally impaired:
There is no need to adjust the dose for the elderly or in patients with mild or moderate liver or kidney function impairment (see PHARMACOLOGY – Pharmacokinetics). Patients with severe liver or kidney dysfunction have not been studied and caution is therefore warranted.

There is no relevant indication for FIRMAGON in women and children.

Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

OVERDOSAGE
There is no clinical experience with the effects of an acute overdose with FIRMAGON. In the event of an overdose the patient should be monitored and appropriate supportive treatment should be given, if considered necessary.

PRESENTATION AND STORAGE CONDITIONS
The following pack sizes are available:

Starter dose (120 mg x 2, 40 mg/mL after reconstitution) – 1 pack contains:
2 vials with 120 mg powder for injection
2 vials with solvent for injection (Water for Injections 6 mL)
2 syringes (5 mL)
2 reconstitution needles (21G 0.8 x 50mm)
2 injection needles (27 G 0.4 x 25mm)

Maintenance dose (80 mg, 20 mg/mL after reconstitution) – 1 pack contains:
1 vial with 80 mg powder for injection
1 vial with solvent for injection (Water for Injections 6 mL)
1 syringe (5 mL)
1 reconstitution needle (21G 0.8 x 50 mm)
1 injection needle (27G 0.4 x 25 mm)

List of excipients
Powder: Mannitol
Solvent: Water for Injections

Special precautions for storage
Store below 25°C.

Chemical and physical in-use stability of the reconstituted product has been demonstrated for 2 hours at 25°C after solvent addition. From a microbiological point of view, once reconstituted, the product should be administered immediately.

Special precautions for disposal
No special requirements for disposal.

NAME AND ADDRESS OF SPONSOR
Ferring Pharmaceuticals Pty Ltd
Suite 2B, Level 2, 802 Pacific Highway
Gordon NSW 2072
Australia

POISON SCHEDULE OF THE MEDICINE
Prescription Medicine

DATE OF TGA APPROVAL
16 February 2010

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au