Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Leuprorelin acetate

Proprietary Product Name: Lucrin Depot, Lucrin XL Depot

Sponsor: Abbott Australasia Pty Ltd

September 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 Strength and New Route of Administration
Decision:	Registration of a new strength: Approved Addition of a new route of administration: Rejected
Date of Decision:	30 July 2010
Active ingredient(s):	Leuprorelin acetate
Product Name(s):	Lucrin Depot, Lucrin XL Depot
Sponsor's Name and Address:	Abbott Australasia Pty Ltd 32-34 Lord Street Botany NSW 2019
Dose form(s):	Depot
Strength(s):	30 mg
Container(s):	Pre-filled dual chamber syringe with single dose, sterile lyophilised microspheres in the front chamber and diluent 1.0 mL in the rear chamber.
Pack size(s):	One
Approved Therapeutic use:	For the palliative treatment of metastatic or locally extensive prostatic cancer (Stages C and D).
Route(s) of administration:	Subcutaneous injection
Dosage:	Subcutaneous injection every six months
ARTG Number:	160467 (Lucrin XL Depot)

Product Background

Leuprorelin acetate is a synthetic nonapeptide analogue of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH). The analogue possesses greater potency than the natural hormone. Leuprorelin acetate acts as an inhibitor of gonadotropin production and is chemically unrelated to the steroids.

Leuprorelin acetate acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Animal and human studies indicate that following an initial stimulation, chronic administration of leuprorelin acetate results in suppression of ovarian and testicular steroidogenesis.

Administration of leuprorelin acetate has resulted in inhibition of the growth of certain hormone-dependent tumours (prostatic tumours in Noble and Dunning male rats and DMBA [7,12-dimethylbenz[α]anthracene - a tumour initiator]-induced mammary tumours in female rats) as well as atrophy of the reproductive organs.

In humans, administration of leuprorelin acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males and oestrone and oestradiol in pre-menopausal females). However, continuous

administration of leuprorelin acetate results in decreased levels of LH and FSH. In males, androgens are reduced to castrate or pre-pubertal levels. In pre-menopausal females, oestrogens are reduced to post-menopausal levels. These decreases occur within a month of initiating treatment and are maintained as long as treatment continues. Consequently, tissues that depend on testosterone including prostate cancer become quiescent.

Lucrin contains the active ingredient leuprorelin acetate and has been approved in Australia since October 1991. It is well established as a treatment for advanced or metastatic prostate cancer, by providing effective androgen suppression to reach plasma concentrations of testosterone below the accepted castration level, established at 50 ng/dL. The current registered formulations of Lucrin comprise a 5mg/mL solution intended for daily subcutaneous (SC) administration (AUST R 29658) and three depot formulations, which provide 1 month (7.5 mg, AUST R 114302), 3 months (22.5 mg, AUST R 114303) or 4 months (30 mg, AUST R 114304) of androgen suppression after a single intramuscular (IM) injection.

Globally, the recommended doses for leuprorelin acetate treatment differ, with countries categorized as either high or low dose markets (Table 1).

Table 1: Available Presentations of Leuprorelin Acetate

	High Dose IM/SC	**Low Dose SC**
1M Depot	7.5 mg	3.75 mg
3M Depot	22.5 mg	11.25 mg
4M Depot	30 mg	-
6M Depot	30 mg	30 mg

The clinical studies included in the original application for the one month (1M) depot formulation supported efficacy and safety with both evaluated doses of 3.75 mg and 7.5 mg. However, the regulatory approach varied as to whether the minimum effective dose of 3.75 mg was approved as for example in Japan, New Zealand and all EU countries except Spain, or the highest effective safe dose of 7.5 mg was chosen, as in the USA, Canada, Australia and Spain. It should be noted that Spain is in the process of aligning its registrations to the low dose formulations approved in the rest of the EU. In addition, whilst no difference was observed between the subcutaneous and intramuscular routes of administration, in territories where the 7.5 mg depot is registered only the intramuscular route of administration is currently included in the approved product label.

Subsequent development of formulations with longer release profiles has logically followed the initial registration, with a dose of 11.25 mg being selected for the three month (3M) depot in low dose markets and 22.5 mg for high dose markets. An additional 30 mg four month (4M) formulation has also been registered only in the high dose markets. Whilst there are no data directly comparing the 3M depot formulations of 11.25 mg and 22.5 mg, indirect comparisons of available clinical data confirm that both formulations are safe and efficacious in the treatment of advanced or metastatic prostate cancer, which is supported by over a decade of use in all major global markets.

Lucrin XL contains leuprorelin embedded in polylactic acid (PLA) microspheres. PLA is a biodegradable polymer and controls the rate of release of the drug. Leuprorelin is also embedded in PLA in the 3- and 4-month Lucrin formulations; however, a higher molecular

weight is used in Lucrin XL to extend the release of leuprorelin. If the proposed 30 mg 6-month formulation is registered, the sponsor will consider withdrawing the 30 mg 4-month formulation to avoid confusion.

Similar registered products are leuprorelin acetate (Eligard) SC, goserelin acetate (Zoladex) SC and triptorelin embonate (Diphereline) IM. Eligard has a 6-month strength.

The current application requested two changes to the conditions of registration. The first was to add a new route of administration (by subcutaneous injection) to the approved route of administration (by intramuscular injection) for:

- Lucrin Depot: leuprorelin acetate 7.5 mg prefilled dual-chamber syringe (AUSTR 114302)
- Lucrin Depot 3-Month: leuprorelin acetate 22.5 mg prefilled dual-chamber syringe (AUSTR 114303)
- Lucrin Depot 4-Month: leuprorelin acetate 30 mg prefilled dual-chamber syringe (AUSTR 114304)

The second was to register a new formulation of leuprorelin, Lucrin XL Depot 6-Month leuprorelin acetate 30 mg prefilled dual-chamber syringe (PDS) to be given by both subcutaneous and intra-muscular injections.

Regulatory Status

An application for Lucrin XL Depot 6-Month 30mg Prefilled Dual-Chamber Syringe has been approved in Austria (29 May 2008), Belgium (1 February 2010), Finland (27 June 2007), France (4 March 2008), Germany (8 July 2008), New Zealand (21 May 2009), Norway (8 January 2008) and Sweden (7 September 2007).

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Leuprorelin acetate is a hygroscopic, white or almost white powder. It has a molecular formula of $C_{59}H_{84}N_{16}O_{12}.C_2H_4O_2$ and a molecular weight of 1269.47. The solubility of leuprorelin acetate in water is more than 75% and less than 0.0001% in ether and hexane.

Drug Product

Lucrin Depot 7.5 mg PDS Injection contains leuprorelin acetate (7.5 mg), gelatin (1.3 mg), poly(lactic-co-glycolic acid) 3:1 polymer (66.2 mg) and mannitol (13.2 mg). The accompanying diluent contains mannitol (50 mg), carmellose sodium (5 mg), polysorbate 80 (1 mg), Water for Injections (1 mL) and glacial acetic acid to control pH.

Lucrin Depot 3-Month PDS Injection contains leuprorelin acetate (22. 5mg), polylactic acid (198.6 mg) and mannitol (38.9 mg). The accompanying diluent contains mannitol (75 mg), carmellose sodium (7.5 mg), polysorbate 80 (1.5 mg), Water for Injections (1.5 mL) and glacial acetic acid to control pH.

Lucrin Depot 4-Month PDS Injection contains leuprorelin acetate (30 mg), polylactic acid (264.8 mg) and mannitol (51.9 mg). The accompanying diluent contains mannitol (75 mg), carmellose sodium (7.5 mg), polysorbate 80 (1.5 mg), Water for Injections (1.5 mL) and glacial acetic acid to control pH.

Lucrin XL Depot 6-Month PDS Injection contains leuprorelin acetate (30 mg), polylactic acid
(270 mg) and mannitol (52.9 mg). The accompanying diluent contains mannitol (50 mg), carmellose sodium (5.0 mg), polysorbate 80 (1.0 mg), Water for Injections (to 1.0 mL) and glacial acetic acid to control pH.

Quality Summary and Conclusions

There were no chemistry or biopharmaceutic issues and the quality evaluator recommended approval.

III. Nonclinical Findings

Introduction

Abbott Australasia Pty Ltd has applied to register a new dosage form of leuprorelin acetate (Lucrin XL Depot), a 6 month 30 mg depot for SC and IM injection. The sponsor is also applying to add the option of administration by SC injection for all existing depot presentations currently approved for IM administration; 7.5 mg, 1 month; 22.5 mg, 3 month; 30 mg, 4 month. In support of this application, nonclinical data comprised 4 studies and included 2 analytical method/validation reports, a pharmacodynamics/pharmacokinetics study following SC administration and a local tolerance study monitoring reactions from IM and SC injections.

Pharmacology

A 9 mg SC injection of the proposed 6 month depot formulation suppressed serum testosterone levels to ≤60 ng/dL for approximately 6 months (compared with >62 ng/dL for control animals). A consistent rate of leuprorelin disappearance from the depot occurred over this time period, maintaining plasma levels of leuprorelin at ≥0.3 ng/mL. Therefor e an SC injection of the proposed formulation at a dose >10 fold higher than that anticipated clinically[1] (on a body surface area [BSA] basis) can suppress testosterone levels for 6 months. However, no data were provided in the nonclinical submission to compare the efficacy of the newly proposed formulation to the currently approved formulations. Thus, the relative efficacy needs to rely solely on clinical data.

Pharmacokinetics

No studies were submitted comparing the pharmacokinetics of leuprorelin following IM and SC administration of approved depots or the new clinical formulation. Within the depot, leuprorelin is encapsulated in poly (lactic-co-glycolic acid) (1 month formulation) or, in all other depots, poly lactic acid microspheres. While previously submitted studies indicated the pharmacokinetic behaviour of leuprorelin in a microcapsule system (poly(lactic-co-glycolic acid) 3:1 polymer) was similar following IM and SC administration in rats, it is unclear if this is the same formulation as the 7.5 mg/1 month Lucrin Depot. Systemic exposure to leuprorelin depends on the rate of release from the site of injection. The different local environments surrounding the depot after SC and IM injection may alter the depot release kinetics and subsequent plasma levels of leuprorelin. In the absence of sufficient nonclinical information, the bioequivalence of SC and IM administration ultimately relies on clinical data.

[1] Assuming masses of 0.2 kg and 50 kg for rats and humans, respectively, and mg/kg to mg/m^2 conversion factors of 6 and 33 for rats and humans, respectively, the dose used in rats was 270 mg/m^2 compared with the proposed clinical dose of 19.8 mg/m^2.

Relative exposure

The pharmacokinetics of leuprorelin following IM administration of the new Lucrin XL Depot 6 month formulation was not assessed in the clinical package. A comparison of the maximal plasma concentration (C_{max}) and the time to maximal plasma concentration (T_{max}) values following SC administration of the new depot with the currently registered IM Lucrin Depot is shown in Table 2. Compared with existing depots, the C_{max} for the 6 month SC depot is 1.6-1.9 times higher, but is still lower than that obtained from the currently-registered leuprorelin SC depots (>102 ng/mL; Eligard Product Information document). However, for a slow release formulation such as this, the area under the plasma concentration time curve (AUC) would be a better parameter for both safety and efficacy assessment. While a human area under the plasma concentration time curve from time zero to 30 days (AUC_{0-30}) of about 83 ng.days/mL was provided in the clinical submission for the 6 month SC depot (30 mg), it is unclear how this exposure compares with that achieved from existing depots. Therefore, toxicological concerns with the new formulation cannot be fully addressed due to insufficient information.

Table 2: Comparison of pharmacokinetic parameters of the new formulation with existing formulations

	LUCRIN DEPOT®[a]		LUCRIN XL DEPOT®[b]
	3 month 22.5 mg (IM)	**4 month 30 mg (IM)**	**6 month 30 mg (SC)**
C_{max} (ng/mL)	49	59	94
T_{max} (h)	4	4	2

[a]*Information obtained from the PI document;* [b]*From Clinical Study EC 403*

Toxicology

Local tolerance

Local irritation of the proposed 6 month formulation was assessed after both SC and IM administration in rabbits. The doses used for SC administration are identical or similar to those of the Lucrin Depot doses; 11.25, 22.5 and 31.5 mg. Only two IM doses were assessed: 22.5 and 45 mg (that is, not the proposed 6 month dose). After SC administration, erythema and nodules were seen at all test-item injection sites. The erythema disappeared after 9 weeks of dosing. There was no apparent dose-related difference in severity. The nodules gradually retracted from 2 weeks post-dose but were still evident at sites that had received 22.5 mg and 31.5 mg, 34 weeks (~8 months) post dose. In contrast, there were no macroscopic findings after IM injection.

At necropsy, red discolouration was observed on Day 2 post-dose and white substance deposition were observed at the majority of treated sites of SC and IM up to 13 and 2 weeks post-dose, respectively. After 2 weeks, light brown hardening was evident in SC sites with brown discolouration noted after 34 weeks. This was not seen in the IM sites. This hardening may indicate a difference in behaviour of the depot after SC and IM administration.

Histopathological examinations revealed a foreign body granuloma at all SC injection sites and the majority of IM injection sites up to 34 weeks after injection. This was accompanied by macrophage migration and inflammatory cell infiltration. Granuloma formation and associated inflammatory reactions appeared to occur with greater severity after SC administration than IM injection. Furthermore, tissue fibrosis was evident at all SC injection sites 34 weeks after treatment but not at this time point after IM injection.

Overall, the local irritation of the newly proposed Lucrin XL Depot formulation was more severe following a single SC injection than following a single IM injection to rabbits. After IM injection, there was limited evidence of tissue damage. In contrast, local reactions after SC administration were more severe with erythema, nodule formation with significant hardening and a more intense inflammatory response. There was also evidence of significant tissue damage with fibrosis observed in all SC-treated animals up to 8 months post-dose.

No local irritation data were provided following SC injection of the currently-approved IM formulations. It is noted that the 3- and 4-month formulations are similar to the new 6-month formulation, but with higher levels of some ingredients. It is therefore reasonable to assume these formulations would be at least as irritating, if not more, than the 6-month depot. No data were provided on the irritation potential of the 1-month depot.

Nonclinical Summary and Conclusions

It is unclear how the systemic exposure (in particular AUC) achieved with the new formulation compares with that from the existing formulations. Therefore an adequate safety assessment could not be performed.

In the local tolerance study, Lucrin Depot XL was generally well-tolerated after IM injection, with limited evidence of tissue damage. In contrast, local reactions after SC administration were more severe and of longer duration with erythema, nodule formation with significant hardening, a more intense inflammatory response and significant tissue damage with fibrosis still evident up to 8 months post-dose.

No local tolerance study was provided following SC injection of the currently approved IM formulations but it is reasonable to assume that the 3- and 4-month depots would be at least as irritating, if not more, after SC injection as the 6-month formulation.

The following are the main outstanding nonclinical issues with the current submission:

- A safety assessment cannot be confidently made due to the absence of adequate comparative pharmacokinetic data of the new depot with currently-registered depots;
- Greater local irritation was observed with the 6 month depot administered via SC compared with IM;
- The potential for local irritation following SC injection of the 1-month formulation remains largely unknown.

Provided the clinical data address the issues indicated, there are no nonclinical objections to the registration of the new dosage form and new route of administration.

IV. Clinical Findings

Introduction

The submission contained a sponsor's *Clinical Overview* and a sponsor's *Clinical Summary* and details of two clinical trials. The two clinical trials were completed four years ago, the last subjects being entered in May and September 2004, and both submitted reports completed on 31 March 2005. Although each is headed "Final Report", Addenda dated 23 June 2005 were prepared for both reports, in which the data were reanalysed at the request of the clinical expert writing the clinical overview for an EU submission, and in response to questions from the German Regulatory Authority.

As well, the most recent Periodic Safety Update Report (PSUR) was submitted.

Proposed registration of a new formulation

The application is to register Lucrin XL, an additional depot formulation designed to provide treatment for a period of 6 months after a single injection. Lucrin XL contains 30 mg of leuprorelin acetate and uses an increase in the molecular weight of the carrier polymer poly(D,L-lactic) acid to achieve a more prolonged release profile. The overview section states "following registration of the 30 mg 6M depot in Australia, consideration will be given to withdrawal of the existing 30 mg 4M depot".

To support the safety and effectiveness of Lucrin XL given by subcutaneous injection, two clinical Studies EC 403 and EC 404 were included in the application.[2]

- Study EC 403 was a randomized, open label, multicentre, parallel group study on the pharmacokinetics and pharmacodynamics of two doses (22.5 mg and 30 mg) of leuprorelin acetate 6M depot formulations.
- Study EC404 was a randomized, open label, multinational, three arm parallel group comparative Phase III study comparing the 22.5 mg and 30 mg 6M depot

[2] The full study numbers were TAP-144-SR (6M) / EC 403 and TAP-144-SR (6M) / EC 404.

formulations to the reference 11.25 mg 3M formulation in 296 patients with prostate cancer over 12 months. The primary objective of this study was safety and tolerability. Secondary study objectives were efficacy (overall response) defined as successful maintenance of serum testosterone suppression to castration levels, without two consecutive elevations of testosterone > 50 ng/dL after the first injection of the study medication until the end of the study at 12 months.

Proposal to change the routes of administration

Two changes are proposed, one to add administration by subcutaneous injection to administration by intramuscular injection, the approved route for the products currently registered in Australia, and the second to add administration by intramuscular injection to the subcutaneous route of administration for the new formulation, Lucrin 6M XL Depot.

The justification for the first change in the route of administration was presented in the sponsor's *Overview*. It used data from what is referred to as a pivotal study, Study TAP-144-SR 02, data from other studies that used both routes of administration and data from a published paper. Each was summarized in a paragraph, and no copies of published papers included.

With respect to the second change, in both studies, EC 403 and EC 404, submitted to support registration of the new formulation, Lucrin XL Depot was administered by the subcutaneous route only. Arguments in favour of the intramuscular route were made by analogy in the above sections of the application.

Efficacy

Study EC403

Study EC403 was a randomized, open label, multicentre, parallel group study on the pharmacokinetics and pharmacodynamics of two doses (22.5 mg and 30.0 mg) of TAP-144-SR 6-Month depot formulations in patients with prostatic cancer. The study was designed to test if testosterone was suppressed for up to 30 weeks after commencing treatment with the new formulation. Furthermore, pharmacokinetic parameters were to be determined and the constant release (after an initial burst effect) assessed over a minimum period of 6 months. Clinical efficacy was determined by prostate-specific antigen (PSA) values and additional investigations as appropriate, and the safety profile by adverse event reporting and monitoring of laboratory safety values.

The primary objective was to show that testosterone serum levels are suppressed to castration level (≤ 50 ng/dL or ≤ 1.73 nmol/L) within 12 weeks of commencing therapy, to determine whether durability of this response can be maintained over 26 weeks and to evaluate after an initial burst effect the mean constant release of leuprorelin acetate by determination of leuprorelin acetate serum levels.

Secondary objectives were:

1. To determine whether luteinizing hormone (LH) and follicle-stimulating hormone (FSH) can be suppressed within 12 weeks after the first injection and this suppression can be maintained until week 26 at least.

2. To classify responses as complete remission, partial remission, stabilization and progression on the basis of clinical examinations and by determination of PSA values and/or scintigraphs, x-rays if necessary and appropriate.

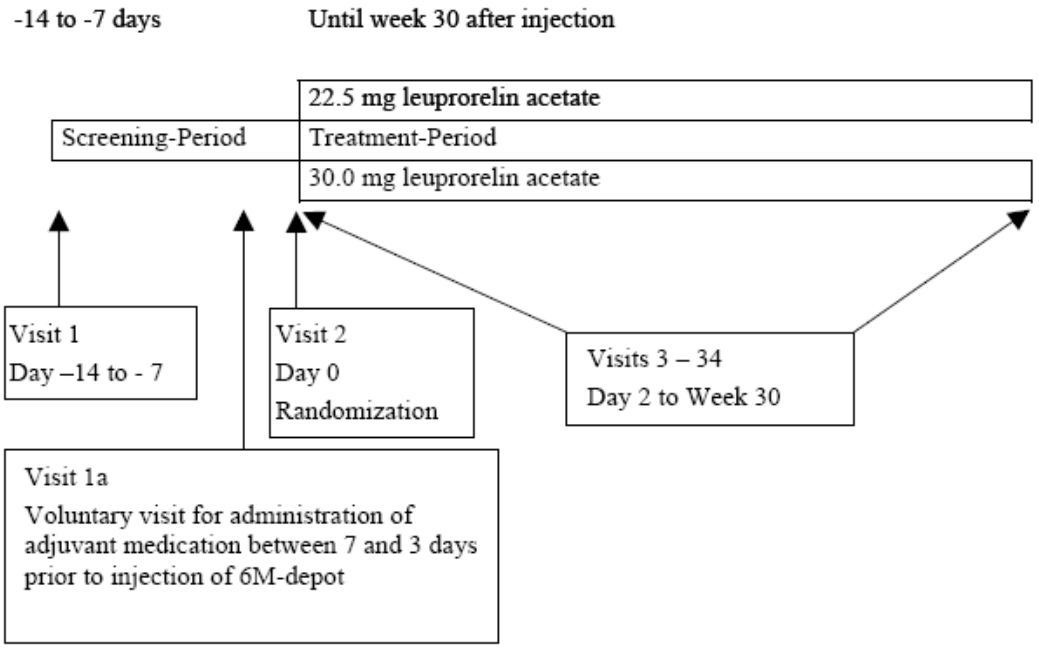
3. To determine the safety of the study treatment by assessing adverse events (AEs), serious adverse events (SAEs), vital signs, physical examination and laboratory tests.

The ethical oversight of the study protocol, of the document of informed consent and of related study information was by Independent Ethics Committees, and the study was carried out in accordance with EU-GCP Guidelines (CPMP/ICH/135/95) effective 17 January 1997, and with the Declaration of Helsinki.

Study Design

This was a randomized, open label, multicentre, parallel group study in subjects with histologically confirmed prostatic cancer requiring hormone ablation. The aim was to compare the pharmacokinetics and pharmacodynamics of two doses (22.5 mg and 30.0 mg) of TAP-144-SR 6-month depot formulation. The scheme of the study is shown in Figure 1.

Figure 1: Schematic of Study Design



The dose for the 6M depot formulation was chosen based on a doubling of the 3M (11.25 mg) marketed formulation for leuprorelin as well as a slightly higher dose of 30 mg to examine the response over time. The study was randomized in order to minimize selection bias. A placebo-controlled study was not chosen, as the application of a placebo was not justified in this subject population. The study was performed as an open-label study, as the syringes for the two doses differed slightly in appearance.

A minimum of 24 subjects per treatment arm with complete data was considered sufficient for the determination of pharmacokinetic parameters.

Efficacy variables

1. Primary efficacy variables: Primary efficacy variables were the testosterone and leuprorelin serum levels, as well as the time to suppression of testosterone serum concentration to castration level (≤50 ng/dL or ≤1.73 nmol/L). The primary efficacy endpoint was suppression of testosterone serum concentration to castration level (≤50 ng/dL or ≤1.73 nmol/L) within 12 weeks after commencement of therapy and maintenance of this response over a period of 26 weeks. Furthermore, the time to suppression of testosterone serum

concentration to castration level was to be evaluated and testosterone and leuprorelin acetate serum levels were to be correlated.

Analysis of the primary efficacy variable also defined responders and non-responders. Responders were defined as those subjects who successfully maintained testosterone suppression (that is without two consecutive elevations of testosterone level >50 ng/dL after the initial expected increase of testosterone levels) until 26 weeks (Visit 30) after injection of study drug. If a testosterone level of £50 ng/dL followed an elevation of >50 ng/dL ("point elevation") after the initial expected increase of testosterone levels, the subjects were still considered responders. Non-responders were those subjects who had at least two consecutive testosterone levels >50 ng/dL after the initial expected increase of testosterone levels. Subjects who received prohibited medications during treatment period were also considered non-responders.

The above analyses were also performed with a testosterone suppression value of 100 ng/dL and response was also evaluated by time point, that is, successful maintenance of testosterone suppression up to the visit of evaluation from injection of study medication.

Evaluator's comment: The latter analysis of suppression down to 100 ng/mL adds little to the overall analysis and is confusing with so many variables and will not be considered further.

2. Secondary efficacy variables: Secondary efficacy variables were to be LH, FSH and PSA serum levels. Secondary efficacy endpoints were as follows:

• Suppression of LH and FSH serum levels within 12 weeks after commencement of therapy and maintenance of this response over a period of 26 weeks.

• PSA stabilization or a decrease in PSA in hormone sensitive prostatic cancer patients.

• Time to LH and FSH suppression.

• Correlation of LH and FSH serum levels to leuprorelin acetate serum concentration.

• Time to re-increase of LH and FSH serum levels at the end of the study.

Evaluator's comments: The Australian Drug Evaluation Committee (ADEC) has considered previously a number of similar depot products that suppress testosterone secretion. Most studies used surrogate markers in addition to other endpoints such as tumour response. At its 191st meeting (12-13 June 1997), the ADEC summarised the following surrogate variables that need to be considered: the time course of testosterone suppression including how quickly this was achieved, whether the flare differed in character from that occurring with the shorter-acting dosage forms, whether maintenance of suppression was as good (as approved comparators), and did the suppression last for the full dose interval? Objective tumour response, performance status, PSA concentrations, and prostatic acid phosphatase (PAP) concentration were regarded as secondary efficacy variables.

The primary and secondary efficacy variables assessed in the present study would be in the ADEC's primary variable category above, and did not include those listed by the ADEC under secondary efficacy variables. Given that the latter have been assessed in the larger second study in this application, the variables used in the present study, Study EC403, are acceptable.

Statistics and Planned Analysis

Standard descriptive sample statistics were applied to summarise continuous variables and ordinal data (arithmetic mean, standard deviation, minimum, median, maximum) including

geometric mean and coefficient of variation derived from log-normally distributed data as appropriate. Categorical data were described using absolute and relative frequencies.

Subject populations analysed: The following data sets were defined for the analysis: The screening population comprising all subjects who gave written informed consent, the full analysis set (FAS) included all subjects who received the study medication and the safety set included all subjects who were included in the FAS. Subjects who received the study medication and provided sufficient data for the parameters under consideration were included in the relevant analyses.

Sample size: The study was exploratory in nature, therefore hypothesis testing was not intended. For the purpose of descriptively evaluating standard pharmacokinetic characteristics, a sample size of 24 evaluable subjects (without any major protocol violation) in each treatment group was considered sufficient, as was the case for the 3-month depot formulation.

Protocol Amendment No. 1, dated 23 June 2003, was incorporated after 34 subjects had been enrolled into the study. The amendment changed the requirements for the diagnosis in the inclusion criteria, for patient withdrawal, included a PSA measurement that had been omitted in the protocol, a change to the study objectives, and a change to the protocol to conform with the Statistical Analysis Plan.

Evaluator's comments: The changes were made mainly in the clinical trial protocol because of errors and omissions. The study as described above includes all corrections and amendments.

Results

Patient disposition

A total of 71 subjects were screened in 10 active centers in Germany. Of these, 62 subjects were randomized and received active treatment. The reasons for screening failure were testosterone level <150 ng/dL (3 subjects), PSA level <1 ng/mL (2 subjects), withdrawal of consent (2 subjects), other cancers requiring acute treatment (1 subject) and other conditions or history considered detrimental to the safety of the subject (1 subject). Fifty-nine (95.2%) randomized subjects completed the study (31 and 28 subjects in the 22.5 mg and 30.0 mg groups, respectively).

Three subjects in the 30 mg treatment group discontinued the study prematurely. All subjects in the 22.5 mg treatment group completed the study. The reasons for premature termination were serious adverse events, tumor progression and planned prostate surgery.

Demographics and Baseline Characteristics

No notable differences were seen in the demographic characteristics of the two treatment groups. In addition, the study report stated that the newly diagnosed patients and those who had relapsed, and their tumour characteristics, were similar in the two groups in the study.

Evaluator's comment

However, the 22.5 mg group had more patients with a better prognosis (65% had a cancer that was moderately differentiated or with moderate anaplasia compared to 48% in the 30 mg group) than the 30 mg group, a difference that might affect clinical response but not the primary efficacy variable of testosterone concentrations.

Although small differences were seen between the two treatment groups for some medical history categories, none were considered clinically relevant. Concurrent medical conditions

were also similar. Although some differences were seen between the two treatment groups for some types of concomitant medications, none of these differences were considered to impact on the results of the study.

A total of 27 (87.1%) subjects in the 22.5 mg group and 29 (93.5%) subjects in the 30 mg group received adjuvant therapy with cyproterone acetate. The primary reason for adjuvant therapy in both treatment groups was the prevention of tumour flare in all patients in the 22.5 mg group and 26 of 29 (89.7%) patients in the 30 mg group.

Data Sets Analysed

Sixty two subjects were found eligible for the study and so were randomized and received the study medication. Thirty one subjects in each treatment group were included in the full analysis set (FAS) and the safety set. No per-protocol analysis was performed. Sub-set analyses included responders and non-responders, and an analysis of patients whose serum concentrations fell to less than 100 ng/mL, rather than 50 ng/mL.

Evaluator's comment

The defined primary endpoint was based on the full analysis set (FAS), that is, on the 62 patients, 31 in each treatment group, treated in the study, although one patient was excluded from the 30 mg group due to "lack of efficacy data". The application also included an Addendum, prepared after the "Final" report, which reanalysed the data and provided individual patient data as well. In the re-analysis of testosterone concentrations, the results included shorter times, namely screening, pre-dose, 30 minutes, 60 minutes , 2, 4, 6 and 24 hours on Visit 2, whereas the "Final Report" began on Visit 3, Day 2. As well, the former table classified results in two groups, £ 50 ng/mL testosterone, and > 50 ng/mL, and the latter as a limit of 50 ng/mL and a limit of 100 ng/mL.

Efficacy Results

Primary Variables

<u>Change in the serum concentrations of testosterone after a single dose of each strength of depot leuprorelin</u>

All subjects (100%) in both treatment groups showed a decrease in testosterone concentration to ≤50 ng/dL within 12 weeks of the injection of the study drug (Table 3). Twenty one (67.7%) subjects in the 22.5 mg and 24 (80.0%) subjects in the 30 mg treatment group maintained this suppression of testosterone until at least Week 26. The difference in rates of responders between the two treatment groups was 12.3% with a 95 % confidence interval (CI) of [-12.8%, 37.3%].

Table 3: Response in Testosterone

Table 11 b. Response in Testosterone (FAS)

Suppression of testosterone ≤50 ng/dL

	Testosterone responders				Difference in rates (30 mg minus 22.5 mg)		
			95% confidence interval [%]			95% confidence interval [%]	
	N	%	lower limit	upper limit	%	lower limit	upper limit
Within 12 weeks (Visit 16)							
22.5 mg treatment group, N=31	31	100.0	98.4	100.0			
30 mg treatment group, N=30	30	100.0	98.3	100.0			
Within 12 weeks and still present after 26 weeks (Visit 30) - Responder							
22.5 mg treatment group, N=31	21	67.7	49.7	85.8			
30 mg treatment group, N=30	24	80.0	64.0	96.0	12.3	-12.8	37.3

Subject 01/610 (30 mg) excluded from the analysis.

Source: End-of-Text Table 15.2.1 - 1 and Appendix 16.2.6 - 1.1

Time to suppression of testosterone concentrations

The mean time to suppression of testosterone (to below 50 ng/dL) in responders was slightly longer in the 22.5 mg group (17.1 days) than in the 30 mg treatment group (14.3 days) (Table 4). No difference was observed for the median time to suppression between the treatment groups. In non-responders, there was no relevant difference in the mean time to suppression of testosterone between the treatment groups (18.9 and 18.2 days for the 22.5 mg and 30 mg groups, respectively), while the 22.5 mg group had a longer median time than subjects treated with 30 mg (21 days and 15 days, respectively).

Table 4: Time to Suppression of Testosterone

Responders

Time to suppression [days]	Responder definition based on 50 ng/dL (primary criterion)					
	Mean	SD	Minimum	Median	Maximum	N
22.5 mg treatment group, N=21	17.1	6.5	7.0	14.0	35.0	21
30 mg treatment group, N=24	14.3	5.9	7.0	14.0	28.0	24

Non-responders

Time to suppression [days]	Responder definition based on 50 ng/dL (primary criterion)					
	Mean	SD	Minimum	Median	Maximum	N
22.5 mg treatment group, N=10	18.9	8.8	7.0	21.0	35.0	10
30 mg treatment group, N=6	18.2	8.3	14.0	15.0	35.0	6

Subject 01/610 (30 mg) excluded from the analysis.

Time course of changes in the concentration of testosterone

Figures 2 and 3 show the mean values of testosterone concentrations plotted against time for responders and non-responders. In the responders, mean testosterone values for both groups were above 400 ng/dL at screening and reduced to around 200 ng/dL at the pre-dose measurement following administration of cyproterone acetate (received by 87.1% and 93.5% subjects for the 22.5 mg and the 30.0 mg group respectively). Mean testosterone levels reached below 50 ng/dL by Week 2 for both groups and remained so till the end of the study at Week 30. In the non-responders, results were similar, but with a testosterone response below 50 ng/dL in the 22.5 mg group being seen one week later at Week 3. Testosterone values above 50 ng/dL were seen at Week 23 for both groups (73.1 ng/dL in 22.5 mg and 52.0 ng/dL in 30.0 mg).

Figure 2: Mean ± SE testosterone concentration versus time curves - responders

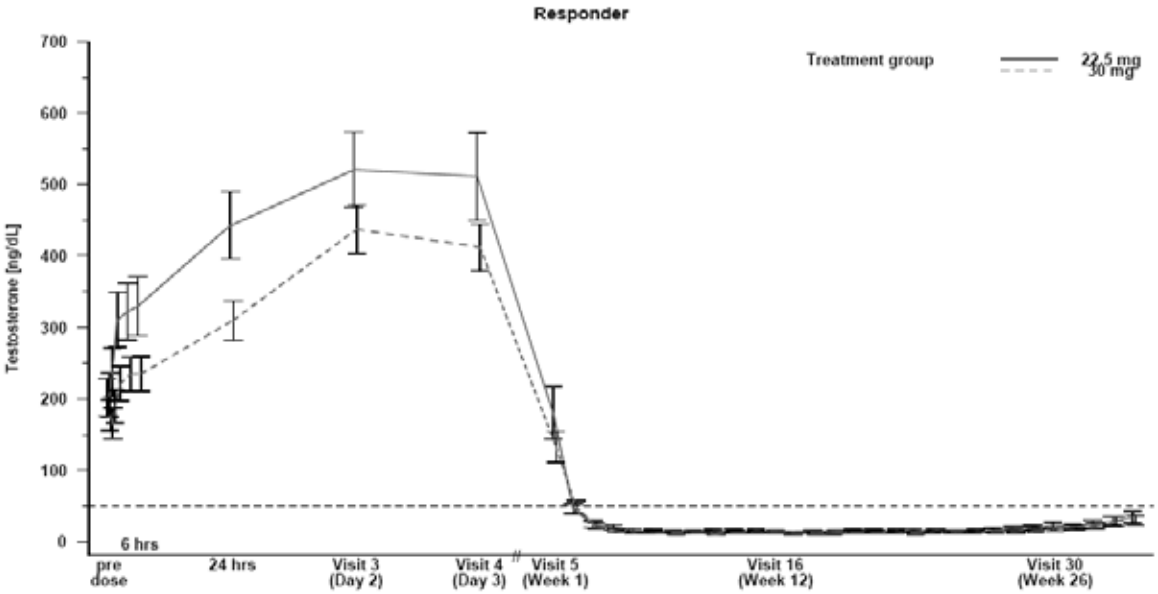
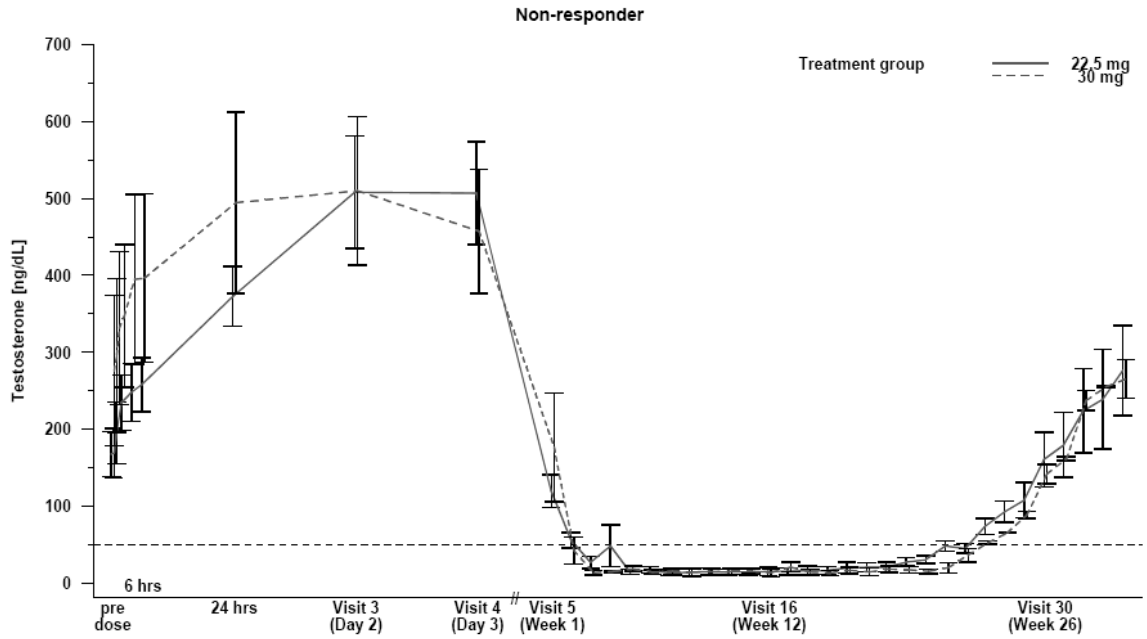


Figure 3: Mean ± SE testosterone concentration versus time curves – non-responders



Serum concentrations of leuprorelin

Leuprorelin serum levels versus time curves showed a similar course in both treatment groups for responders with higher concentrations being seen in the 30 mg group. At

approximately 2 hours post-dose, the first maximum concentration was reached (84260.7± 23032.1 pg/mL in 22.5 mg group, 96042.3 pg/mL ± 28619.4 pg/mL in the 30 mg group). This was then followed by an exponential decrease leading to minimum leuprorelin levels at Visit 5 (Week 1; 170.3 ± 300.4 pg/mL in the 22.5 mg group and 153.3± 344.8 pg/mL in the 22.5 mg group). Thereafter, a smaller second peak was seen at Week 8 and 4 in the 22.5 mg and 30 mg group respectively. The following decrease was slow and levels of leuprorelin below 100 pg/mL were seen at Week 20 for both treatment groups.

In the non-responder group, leuprorelin serum levels versus time curves showed a similar course in both treatment groups. However, in the non-responder group no minimum leuprorelin concentration was observed in the 30 mg group at Visit 5 (Week 1) and levels of leuprorelin below 100 pg/mL were reached earlier in the 30 mg group (Visit 20 (Week 16)) than in the 22.5 mg group (Visit 24 (Week 20)).

The percentage of subjects that had a level of leuprorelin above or below 100 pg/mL for both treatment groups showed a similar pattern. At pre-dose all subjects were below 100 pg/mL leuprorelin except one subject in the 30 mg group (Subject 10/611 had a pre-dose leuprorelin level of 5131 pg/mL). All subjects were then above this level until Day 3, with the trough seen at Day 5. The majority of subjects then had levels of leuprorelin above 100 pg/mL until Week 20. An essentially similar pattern was seen in non-responders.

Pharmacokinetic parameters of leuprorelin

Comparisons of pharmacokinetic (PK) parameters between responders and non-responders revealed a tendency to higher median values for C_{max}, $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}26}$ and $AUC_{0\text{-}30}$ in responders treated with 22.5 mg or 30 mg leuprorelin. There was no difference in t_{max} between responders and non-responders in the 22.5 mg group, whereas t_{max} was longer in responders than in non-responders in the 30 mg group.

Evaluator's comment

The high variability in individual results as shown by the high standard deviation (SD) values (around 50% of mean in some cases), and the lack of statistical comparisons make any firm conclusions unsafe, as does the problem of comparing PK characteristics of responders and non-responders, two groups acknowledged in such studies as not comparable. One striking thing about the PK values is the unit (pg) used, resulting in very high unit numbers.

Correlation between the Concentrations of Testosterone and Leuprorelin

In the figures showing these data, the concentrations of each follow that of the other, except for the responder group at the 22.5 mg dose, where the leuprorelin concentrations fell further from Week 16 to Week 30 compared to the testosterone concentrations. No firm conclusions can be drawn from these results, except that the fall with time in the concentration of both testosterone and leuprorelin is in general similar.

Secondary variables

Time to re-increase of testosterone concentrations

There was no difference in time to re-increase of testosterone between the treatment groups in responders. In non-responders, the mean time to re-increase of testosterone was shorter than that seen for the responder groups.

Time to suppression of LH

There was no relevant difference in the time to suppression of LH between the 22.5 mg and the 30 mg treatment group in responders or non-responders. In the responder group, the time

to re-increase appeared to be longer in the 22.5 mg group than in the 30 mg group. The opposite observation was made in the non-responder group. However, it should be noted that the numbers of subjects in each group are small so the results should be interpreted with caution.

Time to re-increase of LH serum concentration

In the responder group, the time to re-increase appeared to be longer in the 22.5 mg group than in the 30 mg group. The opposite observation was made in the non-responder group. However, it should be noted that the numbers of subjects in each group are small so the results should be interpreted with caution.

Median LH serum concentrations

Median LH serum concentration showed an initial increase (flare-up) followed by an exponential decrease and a plateau phase with more than 50% of the subjects exhibiting LH serum levels below the limit of quantification (LOQ) on most days. A slight re-increase in LH serum levels at the end of the study was caused by the fading effect of leuprorelin, with this effect being more pronounced in the non-responder group.

Correlation of serum concentrations of LH and leuprorelin

Evaluator's comment

The correlation between the 22.5 mg and 30 mg groups, and between the responders and non-responders in these groups, was variable and difficult to interpret

Time to suppression of FSH

There was no relevant difference in the time to suppression of FSH in the responder or non-responder groups between the 22.5 mg and the 30 mg treatment groups.

The time to re-increase of FSH

The time to re-increase of FSH in responders was longer in subjects treated with 22.5 mg compared to subjects treated with 30 mg leuprorelin acetate. In the non-responder group, there was no relevant difference in the mean time to re-increase of FSH between the treatment groups, but subjects treated with 30 mg leuprorelin acetate showed a longer median time to re-increase of FSH than subjects treated with 22.5 mg.

Mean FSH serum concentration

Overall, median FSH serum concentrations showed an initial increase (flare-up) followed by an exponential decrease then a slight re-increase, before a plateau for the rest of the study. In the responder group, the trends over the course of the study were similar in both treatment groups. In the non-responder group, the initial increase in FSH levels was more rapid in the 30 mg group than in the 22.5 mg treatment group and also the maximum FSH concentration was reached slightly earlier in the 30 mg group. No difference between the treatment groups was observed regarding the maximum FSH concentration itself.

During the exponential decrease and the subsequent re-increase, slightly lower FSH levels were obtained in the 30 mg group compared to the 22.5 mg treatment group. No relevant difference between the groups was observed during the plateau phase.

Correlation between FSH and leuprorelin serum concentrations

Evaluator's comment

The correlation between the 22.5 mg and 30 mg groups, and between the responders and non-responders in each group, was variable and difficult to interpret

PSA serum concentrations

An overview of the number and rate of subjects exhibiting a PSA serum concentration≤0.4, >0.4 to ≤1.0, >1.0 to ≤2.0, >2.0 to ≤4.0 and >4.0 ng/mL by visit was provided for responders and non-responders as well as by treatment group. In the responders, median PSA serum concentration showed a slight decrease by Visit 5 (Week 1), which became an exponential decrease at Visit 8 (Week 4) in both treatment groups. The exponential decrease leveled off in a steady state concentration between Visit 24 (Week 20 for the 22.5 mg group) and Visit 20 (Week 16 for the 30 mg group). Steady state concentrations persisted until to the end of the study. Median PSA serum concentration did not show any relevant difference between the treatment groups throughout the study. Examination of the distribution of subjects into categories of PSA levels as mentioned above showed that the majority of subjects were in the above 4 ng/mL category at the start of the study, with a more even distribution across the categories by Weeks 8 to 16. By Week 20 the majority of subjects were in the below 0.4 ng/mL category. A similar pattern was seen for both treatment groups. In non-responders median PSA serum concentration showed very little change at Visit 5 (Week 1) in both treatment groups. However, from Visit 8 (Week 4), an exponential decrease in median PSA was observed in both treatment groups. Minimum concentrations were reached at Visit 24 (Week 20, 22.5 mg group) and at Visit 20 (Week 16, 30 mg group). Thereafter, median PSA levels slightly increased in both treatment groups. Examination of the distribution of subjects into categories of PSA levels as mentioned above showed an even spread across the three categories throughout the study.

Clinical findings

Prostate

The size of the prostate decreased, the firmness lessened and the smoothness improved in responders, with no significant difference between the 22.5 mg and 30 mg groups. The characteristics did not change in either of the dosage groups of non-responders.

Assessment of tumour progression

In the responder group over the course of the study the majority of subjects showed a positive response to treatment, with 19/21 (90.5%) subjects in the 22.5 mg group and 24/24 (100%) subjects in the 30 mg group showing either complete or partial remission by the End of Study. In the non-responder group fewer subjects had an end of study assessment, but for those that did, 5/6 (83.3%) subjects in the 22.5 mg group and 2/2 (100%) subjects in the 30 mg group showing partial remission by the End of Study (no complete remissions were seen in the non-responder group).

Evaluator's Summary and Conclusions from Secondary Variables

The above results are in general agreement with those of the primary analysis, and indicate no serious inconsistencies. The secondary variables for responders compared to non-responders were as expected for a drug of this type. However, the small number of patients and the variability of the measurements prevent any definite conclusions about differences between the 22.5 mg and the 30 mg groups.

Summary of Efficacy Results

- More subjects were classed as responders in the 30 mg group (80.0%) than in the 22.5 mg group (67.7%).
- Rates of 100% testosterone suppression were seen in the 30 mg group from week 4 to week 22.

- A trend was seen in earlier suppression, a more reliable maintenance and a longer duration of response in the 30 mg compared to the 22.5 mg group for the primary efficacy variable of testosterone levels, but the differences were not statistically significant.

Evaluator's conclusions on Study EC403

For the primary parameters, more subjects were classed as responders in the 30 mg group (80.0%) than in the 22.5 mg group (67.7%); and rates of 100% testosterone suppression were seen in the 30mg group from Week 4 to Week 22.

For the secondary parameters, a trend was seen in earlier suppression, a more reliable maintenance and a longer duration of response in the 30 mg compared to the 22.5 mg group for the primary efficacy variable of testosterone levels, but the differences were not shown to be statistically significant. For the parameters of LH, FSH and PSA, a decrease in serum concentrations was seen following treatment, but no notable differences were seen between the two treatment groups.

Serum leuprorelin levels showed an acceptable release of leuprorelin acetate from the depot over the course of the study. Although the geometric mean for $AUC_{0\text{-tlast}}$ values for leuprorelin tended to be lower in the non-responders than in responders in both treatment groups, the differences were not statistically nor clinically significant.

No safety concerns were raised from this study.

Study EC404

Study EC404 was a randomised, open-label, multinational, three-arm, parallel group, comparative, phase III study of TAP-144 SR (3M) and two dosages of TAP-144 SR (6M) in patients with prostate cancer

Leuprorelin acetate is currently available in Australia in three depot formulations (7.5 mg, 3M 22.5 mg, and 4M 30 mg). The study report states that the 3M 11.5 mg (not registered in Australia) showed high efficacy rates in clinical trials in patients with prostate cancer and has led to a better compliance than the daily or monthly injections due to fewer injections and more flexibility. New formulations of a 6M depot of leuprorelin acetate with 22.5 mg and 30 mg leuprorelin acetate have now been developed and are intended for administration on a 6-monthly basis. This new formulation potentially offers advantages in terms of ease of compliance and patients' acceptability and thus indirectly improves the clinical results. In addition, as fewer injections are necessary, a reduction in costs may be seen.

The present study was designed to show the safety and tolerability of three treatments (3M Depot 11.5 mg, 6M XL Depot 22.5 mg and 6M XL Depot 30 mg formulations) in patients either pretreated with GnRH/LHRH analogues and/or antiandrogens for up to 3 months or in patients who are hormone therapy naive and who received one 1M depot injection of leuprorelin acetate within the framework of the study as a pre-treatment (to establish the hormone sensitivity of the prostate cancer). The safety profile and local tolerability at the injection sites were assessed by AE reporting every month and by routine laboratory analyses every three months. Efficacy of the new treatment was assessed by serum testosterone as well as the LH, FSH and PSA levels determined monthly.

Two doses of the 6M depot formulation were chosen to ascertain whether a doubling of the drug concentration of 11.25 mg to 22.5 mg leuprorelin acetate was sufficient to ensure the desired safety and efficacy over the 6-month period of treatment or whether the drug concentration needed to be increased to 30 mg leuprorelin acetate in order to achieve the prolonged efficacy for 6 months with the same safety. A comparative design was appropriate

in order to evaluate the safety and efficacy of the 6M depot formulations in comparison to the 3M depot formulation. The study was randomised in order to minimize selection bias. An open label design was used as it was not possible to blind the "comparator" treatment, and sham injections were not considered appropriate for this patient population. A placebo control was not possible in this study because the application of placebo injections is not justified in patients with prostate cancer for whom active therapy is essential. A treatment duration of 12 months was assumed to be sufficient to demonstrate continuous suppression of the testosterone concentrations to castrate levels, because at least 100 patient-years are necessary for submission of a long-term treatment.

Evaluator's comment

The study has considered those formulations of Lucrin that have been approved and marketed in Europe, and has no references to those approved and marketed in Australia, although the sponsor's letter of application does include the formulations approved in Australia. The relationship between the latter formulations and those used in the present study is as follows: Table 5 shows the "Depot" formulations approved in Australia for intramuscular injection, while "Depot XL" is the new formulation administered by subcutaneous injection in the present study:

Table 5: Comparison of Depot formulations

Formulation	Route	Australia	Study EC403
Lucrin Depot 7.5 mg	IM	Approved	
Lucrin Depot 3-Month 22.5 mg	IM	Approved	
Lucrin Depot 4- Month 30 mg	IM	Approved	
Lucrin Depot 3- Month 11.5 mg	SC	Not registered	Included
Lucrin Depot XL 6- Month 22.5 mg	SC	Not registered	Included
Lucrin Depot XL 6- Month 30 mg	SC	Not registered	Included

Objectives

As stated, the primary study objective was to investigate the safety and tolerability profile of two 6-month depot (6M depot) dosages (22.5 mg and 30.0 mg leuprorelin acetate, respectively) compared to the marketed 3-month depot (3M depot) formulation (containing 11.25 mg leuprorelin acetate) over a treatment period of 12 months. In addition, the efficacy of the three treatments was evaluated.

Evaluator's comment

The objective, as applied to the Australian situation, would be to investigate the safety and tolerability of all three formulations used, with the designated comparator, Lucrin Depot-3M 11.5 mg, regarded as another test formulation.

The ethical oversight of the study protocol, of the document of informed consent and of related study information were by the Institutional Review Boards (IRBs) or Independent Ethics Committees, the study was conducted according to the ethical principles of the Declaration of Helsinki, and the guidelines for Good Clinical Practice.

Study Design

The study was a randomised, open-label, multinational, three-arm, parallel group, comparative, phase III study of patients who either had been pre-treated for up to 3 months

with a GnRH or LHRH analogue and/or antiandrogens (stratum A), or were hormone therapy naive and received one 1M depot injection of 3.75 mg leuprorelin acetate within the framework of the study as pre-treatment (stratum B), with histologically confirmed prostate cancer of any staging and any grading, requiring chemical castration. Patients were enrolled to determine the safety and tolerability profile of two 6-month depot (6M depot) dosages (22.5 mg and 30.0 mg leuprorelin acetate, respectively) compared to a 3-month depot (3M depot) formulation (containing 11.25 mg leuprorelin acetate) over a treatment period of 12 months. In addition, the efficacy of the three treatments was evaluated.

Depending on the treatment group, patients received four injections of 3M depot of 11.25 mg leuprorelin acetate (treatment group 1) or two injections of 6M depot of 22.5 mg leuprorelin acetate (treatment group 2) or two injections of 6M depot of 30.0 mg leuprorelin acetate (treatment group 3) during a treatment phase of 12 months. The dosage of the study drug was not changed during the treatment phase.

The inclusion and exclusion criteria were checked at the screening visit (V1) and patients were assigned to stratum A or stratum B. For patients of stratum B two additional screening visits (V1a and V1b) were performed. At the baseline visit (V2), when the results of all determinations were available, the selection criteria were re-checked. Only patients who met all selection criteria at V2 were included in the treatment phase of the study. An individual patient was only allowed to be included once in this study.

Leuprorelin acetate 3M depot and 6M depot were administered by SC injections. The trial drug was supplied in a dual chamber syringe, one chamber contained the lyophilised microcapsule powder and the other the 1 mL of diluent (suspension medium).

All patients were to receive study treatment for a period of 12 months. The intervals of study drug injections depended on the treatment group the patients were assigned to:

• Treatment group 1: Four injections of 3M depot with 11.25 mg leuprorelin acetate at intervals of three months at baseline (V2), Month 3 (V5), Month 6 (V8), and Month 9 (V11).

• Treatment group 2: Two injections of 6M depot with 22.5 mg leuprorelin acetate at intervals of six months at baseline (V2) and Month 6 (V8).

• Treatment group 3: Two injections of 6M depot with 30 mg leuprorelin acetate at intervals of six months at baseline (V2) and Month 6 (V8).

With the injection of the 1M depot in patients of stratum B (hormone therapy naive patients), patients at risk (for example, metastases of the vertebra and/or positive pelvic lymph nodes with risk of cord compression or acute urinary obstruction) were allowed to receive an overlapping antiandrogen therapy (if indicated) with cyproterone acetate (for example, Androcur tablets with a dosage of 200 mg per day) to prevent the flare-up after the first application of an LHRH analogue. Cyproterone acetate was not supplied by the sponsor because it did not necessarily have to be given to each patient. In patients at risk an overlapping antiandrogen therapy is a routine procedure.

The following medications were to be avoided during the course of the trial: GnRH/LHRH analogues other than the investigational products (goserelin, triptorelin, buserelin); oestrogens; antiandrogens (cyproterone acetate, flutamide, bicalutamide) - for the sole exception refer above for patients of stratum B; cytostatics; cytotoxics; and other investigational drugs.

Variables to be assessed

The overall response to treatment was defined as successful maintenance of suppressed testosterone serum levels without two consecutive elevations >50 ng/dL in the 6M depot groups after first injection of the study medication until the end of the observational period in Month 12 (V14). If a testosterone level of less than 50 ng/dl follows an elevation above 50 ng/dl (point elevation), the patient was still considered a responder. Response was also determined by time point, that is, as a response after the first injection of study medication up to response at Month 12 (V14).

The serum levels of testosterone, luteinising hormone (LH), follicle-stimulating hormone (FSH), prostate-specific antigen (PSA), and of leuprorelin were analysed during the course of study treatment.

For the clinical assessment of prostate cancer and the determination of the clinical response the following methods were used: tumour staging (AJC classification and TNM classification) was performed by the investigator at screening (V1) and at the study termination visit (month 12, V14). The ECOG/WHO performance status assessed at screening (V1) and at the study termination visit (month 12, V14).[3,4,5] To determine complete remission, partial remission, stabilisation and progression of the prostate cancer an assessment on the basis of the EORTC response criteria at the study termination visit (month 12, V14).[6]

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[3] Staging of tumours can be determined using the American Joint Committee (AJC) classification and the TNM Classification of Malignant Tumours (TNM) which describes the extent of cancer in a patient's body.

- **T** describes the size of the tumour and whether it has invaded nearby tissue,
- **N** describes regional lymph nodes that are involved,
- **M** describes distant metastasis (spread of cancer from one body part to another).

[4] ECOG Performance Status. The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:

0 - Fully active, able to carry on all pre-disease performance without restriction
1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5 – Dead

[5] WHO performance scale: The World Health Organisation (WHO) designed the scale which has categories from 0 to 4 as follows:
0 : fully active and more or less as you were before your illness
1 - cannot carry out heavy physical work, but can do anything else
2 - up and about more than half the day; you can look after yourself, but are not well enough to work
3 - in bed or sitting in a chair for more than half the day; you need some help in looking after yourself
4 - in bed or a chair all the time and need a lot of looking after

[6] Response criteria have been developed by the European Organization for Research and Treatment of Cancer (EORTC).

The primary variables for this study were safety variables. Safety variables were adverse events (AEs) which included local tolerability and local injection site reactions, clinical laboratory tests (haematology, blood chemistry and urinalysis), vital signs and physical examinations.

Evaluator's comment

The definitions of the safety parameters and the plan for assessing safety were standard for a study of this type and were acceptable.

Statistics and Planned Analysis

All continuous variables were to be summarised using the standard descriptive statistics (N, mean, standard deviation, minimum, median and maximum). Categorical variables were to be summarised using counts and percentages.

The analysis populations were defined as follows:

Screening population: All patients who were screened.

Safety population: All patients with at least one injection of study medication (3M depot or 6M depot).

Intention-to-treat population (ITT): All patients with at least one injection of study medication (3M depot or 6M depot) and at least one efficacy assessment after the first injection of study medication (3M depot or 6M depot).

The safety evaluations were performed on the safety population. The efficacy evaluations were performed on the intention-to-treat (ITT) population.

The planned total sample size was 250 randomised patients (50 patients assigned to the 3M depot control group, 100 patients assigned to each of the two 6M depot groups). This meant that safety data from 100 patients was to be prospectively collected for one year under the new treatment with each of the 6M depots (22.5 mg and 30.0 mg leuprorelin acetate, respectively). Following the International Council on Harmonization (ICH) note for guidance on population exposure (The Extent of Population Exposure to Assess Clinical Safety; CPMP/ICH/375/95), at least 100 patient years are necessary for submission of a long-term treatment. In addition, with 100 patients an exact binominal test with a nominal 0.05 two-sided significance level has a 90 % power to detect the difference between the null hypothesis proportion $p_o = 0.95$ and the alternative proportion $p_a = 0.85$ (within each 6M depot group). The assumption of the overall response rate for the sample size calculation was based on the results of comparative trials with 3M depot versus 1M depot.

Evaluator's comment

It was noted that the safety assessment of 100 patient years was based on the new 6M formulation (XL Depot), but on two different doses, 22.5 g and 30 g. Pooling of safety data from patients receiving the two doses would be justified if no difference was demonstrated in the frequency or nature of the associated AEs.

A planned safety interim analysis was conducted as soon as the results of visit V8 (6 months after first injection of study medication) of all randomised patients were available, entered in the database and cleaned. For this interim analysis the full analysis as described in the Statistical Analysis Plan (for the 12-month period) was performed. A report was completed but not signed as the timing of the final report was brought forward due to a faster than expected recruitment.

The definition of the variables and the method of their analyses were standard for a study of this type and were acceptable.

Results

Patient disposition

The recruitment of patients started in January 2003 and lasted until September 2003. A total of 340 patients were screened in 42 active study centres in Germany, Austria and Poland. Within this population, 296 patients were randomised and treated with either the 3M or 6M depot formulations. In all, 213 patients completed the study: 37/58 patients (63.8 %) in the 3M depot 11.25 mg group, 87/118 patients (73.7 %) in the 6M depot 22.5 mg group and 89/120 patients (74.2 %) in the 6M depot 30 mg group.

The allocation of patients to the treatment groups is shown in the Table 6.

Table 6: Allocation of patients to the treatment groups

Treatment	Screening population	Safety population	ITT population
No treatment	44	0	0
3M depot 11.25	58	58	58
6M depot 22.5	118	118	117
6M depot 30	120	120	120
T O T A L	340	296	295

Demographics and Baseline Characteristics

The demographics of the safety population were evenly balanced among the three trial groups. The baseline characteristics of previous medications, concurrent conditions and concomitant medications were balanced among the trial groups, and the ECOG PS, mean time since current tumour diagnosis, time since PSA relapse, and the Gleason score at baseline showed no significant differences.[7] Considering the strata, slightly more patients in stratum A (9/10 patients, 90 % in the 3M depot 11.25 mg group, 22/24 patients, 91.7 % in the 6M depot 22.5 mg group and 26/28 patients, 92.9 % in the 6M depot 30 mg group) had a newly diagnosed prostate cancer as compared with patients in stratum B (39/48 patients, 81.3 % in the 3M depot 11.25 mg group, 77/94 patients, 81.9 % in the 6M depot 22.5 mg group and 77/92 patients, 83.7 % in the 6M depot 30 mg group). On the other hand there were slightly more patients in stratum B with a PSA relapse after radiotherapy (about 3 %) or prostatectomy (about 12 %) compared to stratum A (0 % and about 7 %, respectively).

Efficacy Results

Primary variable as defined by testosterone concentrations

The highest response rate was seen in the 30 mg group (combining stratum A and B) with a response rate of 92.5% (111/120 patients), followed by the 22.5 mg group (100/117 patients, 85.5%) and the 3M 11.25 mg group (47/58 patients, 81.0 %) (Table 7). Considering the strata separately, stratum A exhibited the highest response rates at all doses with all response rates of 90 % and higher. In stratum B response rates were lower ranging from 79.2 % to 91.3 %.

Table 8 gives the statistical analysis of response for the ITT population. Two-sided 95 % confidence intervals were calculated for the response rates as well as the pairwise differences between the three treatment groups as illustrated in Table 8.

[7] The Gleason Grading system is used to help evaluate the prognosis of men with prostate cancer. Together with other parameters, it is incorporated into a strategy of prostate cancer staging which predicts prognosis and helps guide therapy. A Gleason score is given to prostate cancer based upon its microscopic appearance. Cancers with a higher Gleason score are more aggressive and have a worse prognosis.

Table 7: Response to treatment (ITT population)

Stratum	Treatment	Responder						Non-Responder		TOTAL	
		<= 50 ng/dL		Single point elevation		TOTAL (responder)		Confirmed elevation		TOTAL	
		N	%	N	%	N	%	N	%	N	%
Stratum A	3M depot 11.25 (n=10)	9	90.0	0	0.0	9	90.0	1	10.0	10	100.0
	6M depot 22.5 (n=23)	17	73.9	4	17.4	21	91.3	2	8.7	23	100.0
	6M depot 30 (n=28)	26	92.9	1	3.6	27	96.4	1	3.6	28	100.0
Stratum B	3M depot 11.25 (n=48)	37	77.1	1	2.1	38	79.2	10	20.8	48	100.0
	6M depot 22.5 (n=94)	69	73.4	10	10.6	79	84.0	15	16.0	94	100.0
	6M depot 30 (n=92)	75	81.5	9	9.8	84	91.3	8	8.7	92	100.0
TOTAL	3M depot 11.25 (n=58)	46	79.3	1	1.7	47	81.0	11	19.0	58	100.0
	6M depot 22.5 (n=117)	86	73.5	14	12.0	100	85.5	17	14.5	117	100.0
	6M depot 30 (n=120)	101	84.2	10	8.3	111	92.5	9	7.5	120	100.0

Table 8: Response to treatment – Statistical analysis (ITT population)

	3M depot 11.25 (n=58)			6M depot 22.5 (n=117)			6M depot 30 (n=120)		
	N	%	95 % Confidence Interval	N	%	95 % Confidence Interval	N	%	95 % Confidence Interval
Responders	47	81.0	68.6 – 90.1	100	85.5	77.8 – 91.3	111	92.5	86.2 – 96.5
	3M depot 11.25 vs. 6M depot 22.5			3M depot 11.25 vs. 6M depot 30			6M depot 22.5 vs. 6M depot 30		
	Difference		95 % Confidence Interval	Difference		95 % Confidence Interval	Difference		95 % Confidence Interval
Response	4.4 %		-8.8 – 17.7	11.5 %		-1.0 – 23.9	7.0 %		-1.8 – 15.8

Evaluator's comment

Although the report stated that the difference in response rate between the two strengths of the 6M XL Depot was 7.0 % in favour of 6M XL Depot 30 mg (95 % CI: -1.8 % to 15.8 %), the evaluator noted that this CI for the difference included zero, and the CIs for the response rates for each formulation overlapped. This was also true for the comparison of the 6M XL Depot 30mg and the 3M Depot 11.5mg, where the CIs for each response rate overlapped, and the CI for the difference, –1.0 to 23.9, contained zero (see Table 8). The evaluator concluded that the three formulations showed effectiveness, with a trend favouring the 6M XL Depot 30mg formulation, but that no statistical significant difference among them was demonstrated in the primary variable.

Time course of testosterone response

Response to treatment defined by the fall in testosterone concentrations was recorded at each monthly visit.

Evaluator's comment

The table provided showed that the number of responders decreased and less frequently increased on sequential visits. The sponsor clarified this by giving two reasons. One was that when a patient had one elevation of testosterone concentration to more than 50 ng/dl on one visit, it was not known whether this will be the only such rise, so the patient would be a responder, or whether such a rise will be repeated and the patient would be a non-responder. Also some patients did not attend all scheduled visits so some responders may be lost from the total number attending on a particular visit. The same data for responders and non-responders are shown in Figures 4 and 5. For responders, the mean values and those represented by the whiskers of the 10th and 90th percentiles lie below the castration level of testosterone from Visit 4 (2nd month) to Visit 14 (12th month).

In these figures, the evaluator presumed the individual points above (outside) the boxes for each formulation are outliers. These points all represent responders, so that high concentrations of testosterone shown could only have occurred once, from the definition of responder.

Figure 4: Testosterone level during the course of the study - responders

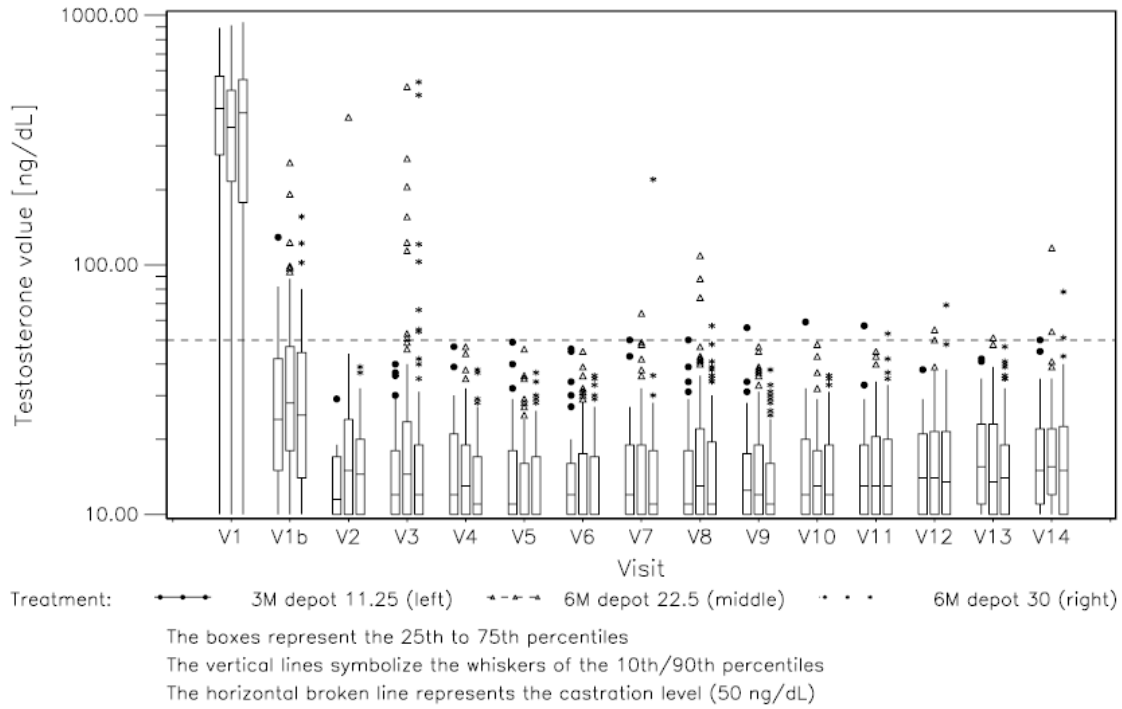
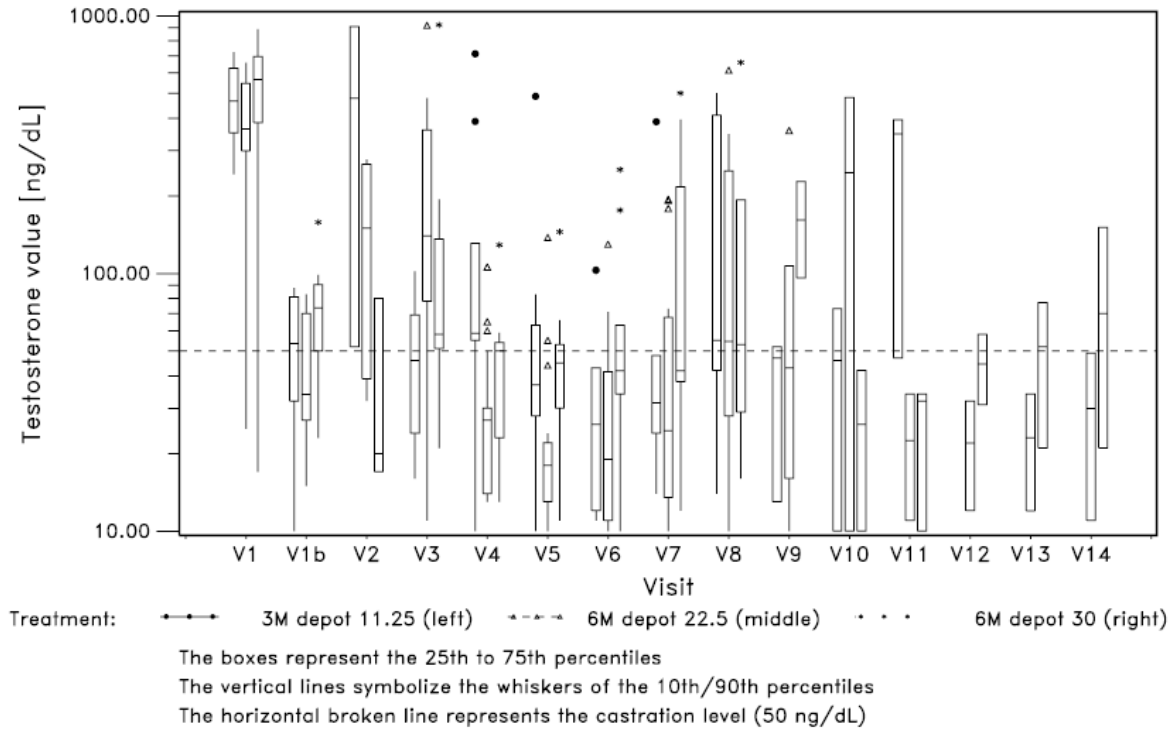


Figure 5: Testosterone level during the course of the study – non-responders



Additional analyses from the Addendum of the frequency and percentages of testosterone levels below 50 ng/dL

Considering all testosterone measurements beginning from baseline, the percentage of samples showing a suppressed testosterone level ≤ 50 ng/dl was 93.5% (n=578) for the 3M depot 11.25 mg group; 94.6% (n=1268) for the 6M depot 22.5 mg group and 96% (n=1291) for the 6M depot 30 mg group at M12, respectively. Excluding samples taken at baseline (V2), the percentage of suppressed testosterone values from M1 to M12 was 93.9% (n= 565), 94.7% (n=1235) and 96.0% (n=1257) for the 3M depot 11.25 mg, the 6M depot 22mg and the 6M depot 30 mg, respectively. From M2 to M12, the percentage of suppressed testosterone samples amounted to 94.3% (n=511), 96.9% (n=1136) and 97.1% (n=1148) for the 3M depot 11.25 mg, the 6M depot 22.5 mg and the 6M depot 30 mg, respectively.

The overall consideration of all testosterone values listed by visit and starting from baseline revealed the following results: at M6 90.4% of samples taken from the 3M depot 11.25 mg group (n=47) showed testosterone values ≤ 50 ng/dl, whereas the percentage was 91.2% (n=103) and 93.9% (n=107) for the 6M depot 22.5 mg and the 6M depot 30 mg group, respectively. At M12, the percentage of suppressed samples was 100% (n=42) for the 3M depot 11.25 mg, 98% (n=96) for the 6M depot 22.5 mg and 96% (n=96) for the 6M depot 30mg group.

Time course of change of PSA concentrations

The observed decrease of PSA levels after the start of the study treatment was similar for the responders in all treatment groups. From Visit 4 to Visit 14 the mean (SD) level of PSA ranged from 1.1 (2.1) – 1.8 (3.1) ng/mL for 3M depot 11.25 mg group, 1.3 (2.9) – 7.1 (56.8)

ng/mL for 6M depot 22.5 mg group and 1.7 (4.2) – 6.5 (39.2) ng/mL for 6M depot 30 mg group. The descriptive analysis of the strata showed no apparent differences.

Regarding the mean PSA levels of the non-responders the time course after the start of study treatment was similar in all three treatment groups (in particular, from V4 to V14 the mean (SD) ranged from 0.9 (0.5) – 21.8 (57.6) ng/mL for 3M depot 11.25 mg group, 1.3 (0.2) – 4.8 (4.8) ng/mL for 6M depot 22.5 mg group and 0.7 (0.6) – 2.1 (3.0) ng/mL for 6M depot 30 mg group). This holds true when comparing the descriptive analysis of the two strata. After a constant decrease of the PSA levels a slight increase could be seen as could be expected for non-responders. This re-increase was not observed for the responders.

Time course of concentrations of leuprorelin

The time courses of the mean leuprorelin levels showed a high degree of variability at all doses. For leuprorelin levels from V4 (2nd month) to V14 (12th month), mean (SD) values ranged from 102.5 (55.8) to 614.4 (1908.8) pg/mL for 3M depot 11.25 mg group, 83.2 (51.9) to 1536.4 (7871.6) pg/mL for 6M depot 22.5 mg group and 119.5 (73.0) to 894.1 (4476.4) pg/mL for 6M depot 30 mg group. No significant differences could be seen between the two strata. There was a temporal relationship between the injection of study medication at V2, V5 (3rd month), V8 (6th month) and V11(9th month) and the clearly increased mean leuprorelin levels at these visits. As well, the maximal values at these visits were extremely high. A possible reason suggested in the study report was that the blood samples of some patients might have been taken after the injection of study medication at the respective visits.

A maximal value of 9.319 pg/mL at V14 was recorded for one patient who received an injection of commercial 3M depot leuprorelin at this visit. The blood sample of this patient had probably been taken after the injection also.

For the mean leuprorelin levels of the non-responders, there were no relevant differences between the treatment groups (in particular, Visit 4 [2nd month]– Visit 14[12th month]: mean (SD) ranged from 67.7 (89.5) – 175.0 (57.3) pg/mL for 3M depot 11.25 mg group, 41.8 (33.1) – 394.2 (836.7) pg/mL for 6M depot 22.5 mg group and 38.3 (38.7) – 241.0 (67.9) pg/mL for 6M depot 30 mg group). The non-responders showed lower leuprorelin levels during the treatment phase compared to the leuprorelin levels of the responders.

Time course of concentrations of LH

For the time course of serum LH levels no differences between the treatment groups could be seen. In responders, the mean (SD) decreased from 5.8 (3.9) - 6.1 (6.5) mU/mL at V1 to 0.3 (0.2) - 0.8 (1.7) mU/mL at baseline (V2), caused by patients of stratum B, who received pre-treatment with 1M depot 3.75 mg leuprorelin acetate. After the first injection of study medication the mean level was suppressed to values of 0.1 (0.1) – 0.4 (0.4) mU/mL until study end.

Time course of concentrations of FSH

The mean (SD) FSH level showed a decrease in all three treatment groups from values between 10.0 (6.8) to 11.9 (15.3) mU/mL at V1 to values between 5.2 (2.1) to 7.2 (2.8) mU/mL during the study. No differences were seen between the treatment groups.

Time course of concentrations of acid phosphatase

Acid phosphatase was evaluated at the screening visit and at the final examination (V14). The results showed there were no relevant differences between the treatment groups at both visits. Mean (SD) values decreased from 5.6 (12.1) to 1.5 (1.4) ng/mL for 3M depot 11.25 mg

group, 4.6 (14.3) to 1.6 (2.8) ng/mL for 6M depot 22.5 mg group and 15.3 (71.3) to 5.6 (20.1) ng/mL for 6M depot 30 mg group.

The majority of patients in each group, that is, 52/58 patients (89.7 %) in the 3M depot 11.25 mg group, 110/117 patients (94.0 %) in the 6M depot 22.5 mg group and 99/120 patients (82.5 %) in the 6M depot 30 mg group showed a normalization of their acid phosphatase level at study end.

Additional analyses from the Addendum

Time course of testosterone, leuprorelin, LH, FSH and PSA levels

The leuprorelin serum levels showed a high variability in all treatment groups. In general, leuprorelin levels tended to be lower in non-responders when compared to responders. LH and FSH as well as PSA levels followed the time course of the testosterone values. For LH, FSH and PSA suppression occurred more slowly during the treatment period and was less pronounced in non-responders when compared to responders.

Clinical response

For the clinical assessment of the tumour response, digital rectal examination (DRE) and assessments of ECOG/WHO performance status and tumour staging according to AJC and TNM were performed at the screening visit (V1) and at the final examination visit (V14 [12th month]). The DRE was also performed after 6 months of therapy (V8). Assessment of the EORTC response criteria was only done at V14.

Results of Digital Rectal Examination

Concerning the size of the prostate, only minor differences between the treatment groups were observed. Whereas about 60 % of the patients in each group had an enlarged prostate at the screening visit (V1), this percentage decreased to about 30 % at the final examination visit (V14).

Evaluation of the prostatic consistency and surface yielded results similar to those observed for the prostate size. For both parameters a definite improvement could be observed. There were no apparent differences between the treatment groups. About 30 % of the patients in each group had a normal prostatic consistency at V1. This proportion increased to about 50 % at V14 (final visit).

Regarding the prostatic surface, about 40 % of the patients in each group had a smooth prostatic surface at V1. This was the case for about 60 % of the patients at study end.

Changes in ECOG/WHO Performance Status

At both time points (V1 and V14) the majority of patients in each group were able to carry out all activity without restriction (grade 0) or were restricted in physically strenuous activity but ambulatory and able to carry out light work (grade 1). There were no differences between the treatment groups. The ECOG/WHO performance status between V1 and V14 did not show any significant changes between the treatment groups.

Response according to EORTC criteria

At the final examination visit (V14) the EORTC response criteria were assessed. The statistical analysis is shown in Table 9.

Overall, the incidence of response at the final examination (V14) was similar among treatment groups. The partial remission rate overall was 51% and the rate of disease stabilization 39%.

Table 9: EORTC response criteria – statistical analysis

	3M depot 11.25 (n=56)			6M depot 22.5 (n=116)			6M depot 30 (n=113)		
	N	%*	95 % Confidence Interval	N	%*	95 % Confidence Interval	N	%*	95 % Confidence Interval
No progression	54	96.4	87.7 – 99.6	110	94.8	89.1 – 98.1	102	90.3	83.3 – 95.0
	3M depot 11.25 vs. 6M depot 22.5			3M depot 11.25 vs. 6M depot 30			6M depot 22.5 vs. 6M depot 30		
	Difference		95 % Confidence Interval	Difference		95 % Confidence Interval	Difference		95 % Confidence Interval
No progression	-1.6 %		-9.2 – 6.0	-6.2 %		-14.8 – 2.5	-4.6 %		-12.2 – 3.1

* Percentages refer to the number of patients with data for V14.

Tumour staging according to AJC and TNM classifications

The tumour staging according to the AJC and TNM classifications was also compared between the screening visit (V1) and the final examination (V14). Regarding the AJC staging, a slight improvement between V1 and V14 could be observed with no relevant differences between the treatment groups. About 22 % of the patients in each group were assessed with "No tumour palpable" (staging A1 or A2) at V1. This percentage increased to about 37-38 % of patients at V14. Concerning the TNM staging, there were no remarkable changes between V1 and V14 in any of the treatment groups.

Optional assessments

A number of optional assessments including hepatic, renal, suprapubic and transrectal sonography, chest X-ray, bone scan, pelvic scan and the CT of the liver were performed on small numbers of patients. Because of the small numbers, comparisons were not meaningful.

Interim analyses and data monitoring

A planned safety interim analysis was performed as soon as the data up to and including visit V8 (6 months after first injection of study medication) of all randomised patients were available, entered in the database, and cleaned. A report was completed but not signed as the timing of the final report was brought forward due to a faster than expected recruitment. The interim report was not included in the application.

Safety

Study EC403

Number of patients exposed and duration of drug exposure

All 62 subjects enrolled in this study received either a single dose of 22.5 mg (31 subjects) or 30 mg (31 subjects) leuprorelin acetate 6-month depot formulation. Three subjects were prematurely discontinued from the study from the 30 mg group. Excluding those subjects who withdrew early, the individual duration of the study ranged from 210 to 225 days (30 to 31 weeks) for all subjects. The mean duration of the study, defined as the time from the injection of study medication to the regular end of study participation or premature termination date (date of Final Examination), was similar for both treatment groups (22.5 mg group: mean 211.1±2.3 [median 210.0] days; 30 mg group: mean 210.1±9.6 [median 210.0] days).

Adverse events

Frequency

Table 10 shows the number of subjects with adverse events (AEs), the number of AEs, and the number of serious adverse events (SAEs) that were reported during the study. The number of subjects with AEs in each treatment group was similar (61.3% in the 22.5 mg group and 64.5% in the 30 mg group), although the number of individual events was higher in the 22.5 mg group (71 events) compared to the 30 mg group (57 events). The proportion of events considered related to study treatment was similar in both groups. There were 7 SAEs in 4 (12.9%) subjects given 30 mg compared and 2 in 2(6.5%) given 22.5mg. The number of SAEs was higher in the 30 mg group (10 events) compared to the 22.5 mg group (5 events), however, the number of subjects experiencing SAEs was similar. Two SAEs, toxic pulmonary oedema and cardiac failure in 1 subject (01/610) were considered related to study treatment. No deaths were reported in either treatment group.

Table 10: Overview of adverse events and serious adverse events

	Treatment group 22.5 mg N=31		Treatment group 30 mg N=31	
	Events (%)	Subjects (%)	Events (%)	Subjects (%)
AE	71	19 (61.3%)	57	20 (64.5%)
Related	29		27	
Not related	42		30	
Mild	39 (54.9%)		21 (36.8%)	
Moderate	30 (42.3%)		29 (50.9%)	
Severe	2 (2.8%)		7 (12.3%)	
Leading to discontinuation	0	0 (0.0%)	3	0 (0.0%)*
SAE	5	3 (9.7%)	10	4 (12.9%)
Related	0		2	
Not related	5		8	
Leading to discontinuation	0	0 (0.0%)	3	0 (0.0%)*
Deaths	0	0 (0.0%)	0	0 (0.0%)

Nature of AEs by System Organ Class and Preferred Term

Tables 11 shows the nature of the AEs occurring in 2 or more subjects in the Safety Population.

The AEs occurring most frequently in more than 20% of subjects in any treatment group by System Organ Class (SOC) were *Vascular Disorders*, *General Disorders and Administration Site Conditions* and *Infections and Infestations*. The high incidence of *Vascular Disorders*

was due entirely to events of flushing (hot flushes) and the incidence of *General Disorders and Administration Site Conditions* were largely due to fatigue and injection site reactions (see below).

The most frequently observed AEs by preferred terms were flushing, injection site erythema, injection site induration and erectile dysfunction. With the exception of vertigo, headache, bladder and urinary tract infections, all of the commonly reported AEs in this study are reported side effects of treatment with LHRH analogues like leuprorelin acetate when administered by depot injection. All events occurred with similar incidence in both treatment groups with the exception of flushing and dysuria, which occurred more frequently after administration of the 22.5 mg depot. The report noted that as the overall population size was small, it was difficult to attribute a true treatment effect to this difference.

With regard to severe AEs, 4 subjects in the 30 mg group reported 7 severe events compared to 2 subjects reporting 2 severe events in the 22.5 mg. However, no severe events were reported in more than a single subject in the 30 mg group. Both severe events in the 22.5mg group were of erectile dysfunction, an expected side effect of lowering testosterone levels with LHRH analogue therapy.

All AEs, which were assessed as related to study drug, were events known to be side effects of leuprorelin acetate depot treatment, with the exception of serious cardiac failure with pulmonary edema reported in a single subject in the 30 mg group and one event of increased appetite (30 mg group).

Table 11: AEs occurring in 2 or more subjects by Preferred Term in order of descending frequency

Subjects with AEs by preferred term (a)	Treatment group 22.5 mg N=31	Treatment group 30 mg N=31	Total N=62
	Subjects (%)	Subjects (%)	Subjects (%)
Any adverse event	19 (61.3%)	20 (64.5%)	39 (62.9%)
Flushing	11 (35.5%)	6 (19.4%)	17 (27.4%)
Injection site erythema	5 (16.1%)	4 (12.9%)	9 (14.5%)
Erectile dysfunction NOS	3 (9.7%)	3 (9.7%)	6 (9.7%)
Injection site induration	3 (9.7%)	3 (9.7%)	6 (9.7%)
Fatigue	2 (6.5%)	3 (9.7%)	5 (8.1%)
Dysuria	4 (12.9%)	0 (0.0%)	4 (6.5%)
Nasopharyngitis	2 (6.5%)	1 (3.2%)	3 (4.8%)
Nocturia	2 (6.5%)	1 (3.2%)	3 (4.8%)
Pain in extremity	3 (9.7%)	0 (0.0%)	3 (4.8%)
Vertigo	3 (9.7%)	0 (0.0%)	3 (4.8%)
Urinary tract infection NOS	2 (6.5%)	0 (0.0%)	2 (3.2%)
Headache	2 (6.5%)	0 (0.0%)	2 (3.2%)
Bladder infection NOS	0 (0.0%)	2 (6.5%)	2 (3.2%)

Parentheses indicate percentages of subjects.
(a) A subject who reported 2 or more AEs within the same preferred term was counted only once for that term.

Injection Site Reactions

Table 12 shows the frequency of these AEs using preferred terms. The overall incidence of injection site reactions was the same in both groups with 5 subjects (16.1%) affected in each group. All but one of these (in the 30.0 mg group) experienced injection site erythema. In addition, induration was seen in 9.7% of subjects in both groups. Other injection site reactions occurred in only single subjects. Local tolerability therefore appeared to be equivalent for both doses of the 6M depot formulation.

Table 12: Incidence of injection site reactions by Preferred Term

	Treatment group 22.5 mg N=31		Treatment group 30 mg N=31		Total N=62	
	Events	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)
Any injection site reaction AE	9	5 (16.1%)	9	5 (16.1%)	18	10 (16.1%)
Injection site erythema	5	5 (16.1%)	4	4 (12.9%)	9	9 (14.5%)
Injection site induration	3	3 (9.7%)	3	3 (9.7%)	6	6 (9.7%)
Injection site abscess	0	0	1	1 (3.2%)	1	1 (1.6%)
Injection site pain	1	1 (3.2%)	0	0	1	1 (1.6%)
Injection site reaction NOS	0	0	1	1 (3.2%)	1	1 (1.6%)

Deaths, other serious adverse events, and other significant adverse events

There were no deaths reported during the study. Since a depot formulation was used, subjects could not be withdrawn from treatment. However two subjects in the 30 mg group prematurely terminated the study due to SAEs, one due to femur fractures (right and left), wound infection and gastrointestinal hemorrhage, and the second due to prostate cancer progression, bone metastases progression and an intraorbital tumor.

Clinical Laboratory Evaluations

Laboratory parameters did not show any relevant changes from baseline to the final examination in either treatment group, and no relevant differences between subjects treated with 22.5 mg and 30 mg leuprorelin acetate were observed. Except for haemoglobin concentration, at the final examination, similar numbers of subjects in both groups had laboratory values outside the normal range after having normal values at baseline. Three of 19 (15.8%) and 12 of 21 (57.1%) subjects in the 22.5 and 30 mg treatment group, respectively, who had normal haemoglobin at baseline, had values below the reference range at the final examination.

Study EC404

Patient Exposure

Study duration was defined as time from first injection of study medication to regular end of study participation or premature termination. Treatment duration was defined as time from first injection of study medication to 3 months or 6 months after last injection. Exposure was equivalent between the three treatment groups (Table 13). The minimum treatment duration of 41 and 69 days shown for the 6M depot groups was caused by deaths.

The number of injections of study medication by visit for the different treatment groups is shown in Table 14.

Table 13: Extent of exposure to investigational products

Duration	Treatment	Extent of exposure [days]					
		N	Mean	SD	Min	Median	Max
Study duration	3M depot 11.25 (n=58)	58	306.6	97.5	16	359.0	374
	6M depot 22.5 (n=118)	118	329.8	70.1	41	359.0	435
	6M depot 30 (n=120)	120	327.4	77.8	33	360.0	415
Treatment duration *	3M depot 11.25 (n=58)	58	304.5	99.2	90	359.0	370
	6M depot 22.5 (n=118)	118	329.0	71.4	41	360.0	368
	6M depot 30 (n=120)	120	329.0	70.5	69	360.0	364

* based on assumption that per 3M depot = 90 days exposure and per 6M depot = 180 days exposure

Table 14: Number of study medication injection by visit and treatment group

Treatment	Number of injections				
	Visit 2	Visit 5	Visit 8	Visit 11	T O T A L
3M depot 11.25 (n=58)	58	50	47	42	197
6M depot 22.5 (n=118)	118	0	99	0	217
6M depot 30 (n=120)	120	1	100	0	221

Adverse Events

Overview

An overview of AEs during treatment phase, their relationship to study medication and severity, withdrawals due to AEs, SAEs and deaths is given in Table 15.

The study report states that overall the incidence of AEs (calculated as ratio of the number of AEs and the number of patients in each treatment group) was similar in all treatment groups as was the percentage of patients who experienced AEs. The incidence of AEs considered to be related to study medication (defined as definite, probable, possible or unknown) was similar between the three groups.

With regard to severity of AEs, 7/157 AEs (4.5 %), 17/315 AEs (5.4 %) and 38/352 AEs (10.8 %) were considered severe in the 3M 11.25 mg, 6M 22.5 mg and 6M 30 mg groups respectively. Thus there was an increased incidence of severe events with increasing dose.

Overall the number of patients withdrawn due to AEs was low (9/296, 3.0 %), and was due to fatal serious AEs (SAEs) with two exceptions in the 6M 30 mg group. A total of seven patients (2.4 %) died during the treatment period, one during pre-treatment and one after withdrawal from the study. The incidence of SAEs was higher in the 6M 30 mg group. However, the investigators considered all SAEs in all groups to be unrelated to study treatment.

Table 15: Overview of AEs and SAEs during treatment phase

	3M depot 11.25 (n=58)			6M depot 22.5 (n=118)			6M depot 30 (n=120)			T O T A L (n=296)		
	Event	Patient		Event	Patient		Event	Patient		Event	Patient	
	N	N	%	N	N	%	N	N	%	N	N	%
AEs	157	45	77.6	315	98	83.1	352	95	79.2	824	238	80.4
related AEs	48			86			98			232		
not related AEs	109			229			254			592		
mild	101			194			192			487		
moderate	49			104			122			275		
severe	7			17			38			62		
AEs leading to withdrawal		2	3.4		2	1.7		5	4.2		9	3.0
SAEs	11	7	12.1	17	14	11.9	27	19	15.8	55	40	13.5
related SAEs												
not related SAEs	11			17			27			55		
SAEs leading to withdrawal		2	3.4		2	1.7		3	2.5		7	2.4
Deaths		2	3.4		2	1.7		4	3.3		8	2.7

Patient : number and percent of patients reporting events
Event : number of events
Related : definite, probable, possible, unknown (as per investigator)
(Table 14.3.2.3)

AEs by System Organ Class (SOC)

Adverse events were classified by SOC for the 3M and 6M depot groups, reported by more than 2 % of patients in any of the three treatment groups. In total, AEs from the SOCs *Vascular Disorders* (143/296 patients, 48.3 %), *General Disorders and Administration Site Conditions* (57/296 patients, 19.3 %) and *Infections and Infestations* (57/296 patients, 19.3 %) were reported most frequently. The occurrence of *General Disorders and Administration Site Conditions* was higher in the two 6M depot groups as compared with the 3M depot group. This represented an increase in the number of injection site reactions (see below for further details). Small differences were observed between the groups for some other SOCs. However, the overall incidence of events for these SOCs was small, and the differences were not considered to be significant.

AEs with preferred terms (PTs) occurring in 5% or more of patients

Adverse events which were reported by 5 % or more of patients in any of the treatment groups, classified by SOC and PT, are presented in Table 16. Overall, the most commonly reported AEs were flushing (110/296 patients, 37.2 %) and hypertension (52/296 patients, 17.6 %), accounting for the high number of *Vascular Disorders* reported. Dizziness, nocturia, sweating, flushing and hypertension are well-known side effects of therapy with LHRH analogues like leuprorelin acetate, so the occurrence of these AEs during the study was expected. The incidence of dizziness, nocturia, sweating and flushing appeared to be higher in the 3M treatment group compared to the two 6M groups, whereas there appeared to be a small increase in the incidence of hypertension with increasing dose (8/58 patients, 13.8 %, 19/118 patients, 16.1 % and 25/120 patients, 20.8 % respectively).

Table 16: AEs reported in more than 5% of patients in any treatment group, stratified by SOC and PT

SOC decode	Preferred term	3M depot 11.25 (n=58)		6M depot 22.5 (n=118)		6M depot 30 (n=120)		T O T A L (n=296)	
		N	%	N	%	N	%	N	%
Gastrointestinal disorders	Constipation	3	5.2	3	2.5	3	2.5	9	3.0
General disorders and administration site conditions	Injection site erythema	1	1.7	7	5.9	6	5.0	14	4.7
	Injection site induration	2	3.4	1	0.8	7	5.8	10	3.4
	Injection site reaction NOS	3	5.2	3	2.5	4	3.3	10	3.4
Infections and infestations	Nasopharyngitis	1	1.7	11	9.3	5	4.2	17	5.7
Metabolism and nutrition disorders	Diabetes mellitus NOS	2	3.4	8	6.8	7	5.8	17	5.7
	Hypercholesterolaemia	7	12.1	15	12.7	9	7.5	31	10.5
Musculoskeletal and connective tissue disorders	Back pain	3	5.2	8	6.8	6	5.0	17	5.7
Nervous system disorders	Dizziness	4	6.9	4	3.4	2	1.7	10	3.4
Renal and urinary disorders	Nocturia	3	5.2	1	0.8	4	3.3	8	2.7
Skin and subcutaneous tissue disorders	Sweating increased	6	10.3	9	7.6	8	6.7	23	7.8
Vascular disorders	Flushing	25	43.1	44	37.3	41	34.2	110	37.2
	Hypertension NOS	8	13.8	19	16.1	25	20.8	52	17.6

Injection site reactions

Table 17 shows the incidence of injection site reactions (ISRs) by preferred terms. The most frequently documented events were ‘injection site erythema’ (14/296 patients, 4.7 %), ‘injection site induration’ (10/296 patients, 3.4 %) as well as ‘injection site reaction NOS’ (9/296 patients, 3.0 %). About two thirds of the observed local skin reactions were assessed as of mild severity and none of the events were assessed as severe.

Considering the overall number of injections received by each treatment group, the relative rate of injection site reactions was higher with the new 6M depot formulations compared to the 3M depot, with the highest rate observed in the 6M depot 30 mg group (2.0 %, 8.8 % and 11.8 % respectively).

Table 17: Injection site reactions – number and percent of patients by PT, in descending frequency

Preferred term	T O T A L (n=296)		3M depot 11.25 (n=58)		6M depot 22.5 (n=118)		6M depot 30 (n=120)	
	N	%	N	%	N	%	N	%
Injection site erythema	14	4.7	1	1.7	7	5.9	6	5.0
Injection site induration	10	3.4	2	3.4	1	0.8	7	5.8
Injection site reaction NOS	9	3.0	2	3.4	3	2.5	4	3.3
Injection site inflammation	6	2.0	.	.	2	1.7	4	3.3
Injection site pain	5	1.7	.	.	3	2.5	2	1.7
Injection site swelling	2	0.7	.	.	.	.	2	1.7
Injection site dermatitis	1	0.3	.	.	1	0.8	.	.
Injection site pigmentation changes	1	0.3	.	.	1	0.8	.	.

Deaths, other serious adverse events, and other significant adverse events

Four patients experienced four SAEs during treatment with 1M depot, all of which were considered unrelated to treatment. In total, 40 patients experienced 55 SAEs during the study period.

Deaths

During the treatment period a total of 8 of 296 patients (2.7 %) died, two in the 3M depot 11.25 mg group, two in the 6M depot 22.5 mg group and four in the 6M depot 30 mg group as follows:

3M depot 11.25 mg group – one patient died from an acute abdomen due to spontaneous perforation, and one patient died from cardiac failure;
6M depot 22.5 mg group – one patient died from suicide after worsened depression; one patient experienced sudden cardiac death;
6M depot 30 mg group- one patient experienced SAEs of urosepsis, intestinal diverticulitis and hydrocholecystitis which all contributed to death; one patient died from an arrhythmia. (Note: death occurred after the subject had been withdrawn from the study); one patient (6M depot 30 mg group) experienced sudden cardiac death; one patient died from the indication being investigated (metastatic prostate cancer).

All of these fatal events were reported to be unrelated to the study medication.

Additionally, one screening failure died from sudden natural death. This event was assessed as being not related to the pre-treatment with 1M depot leuprorelin acetate.

Additional safety analyses requested and presented in the Addendum to the Final Report

A request was made for results showing the duration of treatment for those patients who died during the study or within 30 days after termination of the study. This showed no clear association of death with the duration of treatment. Another request was to clarify a possible

causal relationship for the AEs of anemia and hypertension with the trial drugs. A table was provided which showed that there were no safety concerns on this point.

Other serious adverse events

Overall, 7/58 patients (12.1 %) in the 3M depot 11.25 mg group reported 11 SAEs, 14/118 patients (11.9 %) in the 6M depot 22.5 mg group reported 17 SAEs and 19/120 patients (15.8 %) in the 6M depot 30 mg group documented 27 SAEs. None of the 55 SAEs was assessed by the investigators as being related to the study medication. However, one event (worsening of gynaecomastia) was assessed as possibly related by the sponsor.

Of the 44 non-fatal SAEs, the outcome was reported as 'recovered' for 39 events, as 'improved' for 1 event and as 'unchanged' for 4 events. Regarding the time course of the occurrence of the SAEs during the study no pattern could be observed in any treatment group.

A closer analysis of the SAEs categorized by SOC or preferred term (PT) revealed that there were no relevant differences between the treatment groups. On a PT basis, none of the events were reported for more than 1 patient in any of the treatment groups, except for 'urinary retention', which was documented for 2 patients in the 6M depot 30 mg group.

A total of 3 patients in the 6M depot 30 mg group had SAEs during pre-treatment with 1M depot. These were patients who suffered from worsening of gynaecomastia, worsening of lower urinary tract symptoms with catheterization (urinary retention), and suspected transient ischaemic attack, respectively. None of these events were assessed by the investigators as being related to the 1M depot medication.

Adverse events leading to patient withdrawal from the study

Overall, 9/296 patients (3.0 %) were withdrawn from the study due to AEs (2/58, 3.4 % in the 3M depot 11.25 mg group, 2/118, 1.7 % in the 6M depot 22.5 mg group and 5/120, 4.2 % in the 6M depot 30 mg group). Seven of these events were fatal. One patient withdrew from study due to AEs of headache, vertigo which occurred 20 weeks after the first injection of 6M depot 30 mg and sleep disorder ("hyposomnia") which occurred 16 weeks after the first injection of 6M depot 30mg. All three events were of moderate intensity. For all three events the investigator assessed a possible causal relationship to the study medication. One patient withdrew from the study due to bone metastases, which occurred 40 weeks after the first injection of 6M depot 30 mg. The event was of moderate intensity and was assessed as not related to the study medication.

Clinical Laboratory Evaluation

For all haematology and biochemistry variables, mean changes from baseline to last value were small and similar across the treatment groups with no meaningful differences seen.

Although numerous patients exhibited shifts from normal values at baseline to low or high at last value in many haematological and biochemical variables, these changes were consistent with the disease under treatment and no meaningful differences were seen between the three treatment groups for any variables.

No apparent differences between the treatment groups could be observed in numbers of individual patients with clinically significant abnormalities in any haematological or biochemistry variables.

Evaluator's Safety Conclusions from Study EC 404

• Overall, the incidence of AEs and the number of patients experiencing AEs was similar between the three groups. However the incidence of severe AEs increased with dose – 4.5%,

5.4% and 10.8% in the 3M 11.25, 6M 22.5, and the 6M30mg groups, a clinically significant increase being seen in the latter group. No statistical evaluation was provided.

• Overall, the most commonly reported AEs were flushing (110/296 patients, 37.2 %) and hypertension (52/296 patients, 17.6 %). In addition, dizziness, nocturia and sweating were also commonly reported. For all of these events, the highest rate was seen after 3M depot 11.25 mg treatment, with the exception of hypertension where there appeared to be a small increase in incidence with increasing dose (8/58 patients, 13.8 %, 19/118 patients, 16.1 % and 25/120 patients, 20.8 % respectively).

• Injection site reactions were commonly reported AEs, none of which were reported to be severe. The number of reactions reported and the number of patients experiencing them increased with increased dose. Thus the overall injection site reaction rate was 2.0 %, 8.8 % and 11.8 % for the 3M depot 11.25 mg, 6M depot 22.5 mg and 6M depot 30 mg groups respectively.

• Overall the number of patients withdrawn due to AEs was low (9 of 296; 3%). Seven were due to fatal but unrelated SAEs and two due to non-serious AEs.

• A total of nine patients died during the study, one during the screening period after 1M depot administration, and a further 2, 2 and 4 patients respectively from the 3M depot 11.25 mg, 6M depot 22.5 mg and 6M depot 30 mg groups. None of the events were considered related to treatment.

• One serious AE of worsened gynaecomastia, (3M depot 11.25 mg treatment) was considered possibly drug-related by the sponsor. No other serious AEs were considered related and no pattern or difference between the treatment groups was observed.

• No significant findings or apparent differences between the treatment groups were observed in either mean changes from baseline to last value or numbers of individual patients with clinically significant abnormalities in any haematological, biochemistry or vital signs variables. No significant changes were noted on physical examinations. The data did confirm that a number of clinical laboratory abnormalities results from the use of leuprorelin, as described in the approved product information.

Periodic Safety Update Report (PSUR)

The PSUR of 302 pages was the 21st report, and covered the period from 1 February 2008 to 31 July 2008. The report stated that cases of a serious unlisted ADR, namely interstitial lung diseases, which has been kept under close surveillance, were cumulatively reviewed. The review did not provide sufficient evidence to support a causal relationship between interstitial lung diseases and the use of leuprorelin acetate. From the data obtained during the investigation period and cumulative experience to date, the sponsor did not consider it necessary to make any revision of the Core Company Safety Information at present.[8] However, the sponsor stated it will continue to monitor all suspected adverse reactions and will, if necessary, take such actions as are appropriate in the light of any new findings, in order to ensure the safe and proper use of leuprorelin acetate worldwide.

[8] A Company Core Safety Information (CCSI) is a subset of the Company Core Data Sheet (CCDS) which contains all relevant safety information that a company requires to be listed in all countries where the drug is marketed. It serves as reference information for determining the "listedness" of an adverse reaction.

Evaluator's comment

During the investigation period, there were a total of 29 cases with fatal outcome. Of these, no case reports indicated new unexpected organ toxicity. The individual case reports were provided in summary. Ten reported cases of interstitial lung disease were reported, and from the descriptions of the cases and the analysis given in the report, the evaluator agreed with the above conclusion

Clinical Summary and Conclusions

Proposed new formulation of 6M XL Depot 30mg

Both studies were well designed, well conducted and the data well presented. However the interpretation of the data led the evaluator to different conclusions from those in the application.

Efficacy

The 3M 11.25mg, the 6M 22.5mg and the 6M 30mg depot formulations were all effective in studies EC 404 and the latter two formulations in study EC 403, as judged by international criteria including those accepted by the ADEC. Although a trend was present suggesting greater efficacy of the 30mg preparation, this was not shown to be statistically nor clinically significant in either study.

Safety

Severe adverse events were more frequent with the 30 mg preparation (10.8%) than with the 22.5 mg preparation (5.4%), as were the most commonly reported AEs of dizziness, nocturia and sweating, and the frequency of injection site reactions. Both the 6M 22.5 mg and the 6M 30 mg formulations were associated with a significantly higher incidence of injection site reactions, 8.8% and 11.8% respectively, compared to 2.0% for the 3M 11.25 mg formulation.

Conclusions

The evaluator concluded that the new formulation proposed for registration in this application is effective, but was not shown to be more so than the 22.5 mg preparation, and was associated with greater toxicity. Therefore the evaluator was unable to recommend approval of the 30 mg preparation when an equally effective and less toxic preparation, the 22.5 mg formulation, is available. Compared to the 3 monthly injection, the 30 mg 6 monthly injection was associated with a 6-fold increase in injection site reactions. Fully informed patients would therefore need to choose between receiving twice as many injections with the 3M preparation, but with one-sixth the chance of having an injection site reaction, compared to the 6M formulations.

One option is that the TGA might ask the sponsor to consider marketing the 22.5 mg formulation instead of the 30 mg formulation. A second option is to ask the sponsor to conduct a comparative study of the 30 mg and the 22.5 mg formulations to shown convincingly that the greater efficacy of the former, if it exists, is acceptable given the greater toxicity associated with the 30mg dose.

Request to approve administration of the new formulation, Lucrin XL Depot 30 mg by intra-muscular injection in addition to the subcutaneous route for which data was provided

The argument presented

The request was made in the letter of application and supported by arguments presented in an overview of the application. No clinical data were presented to show that intramuscular injection of the new formulation (Lucrin XL Depot 6-month PDS Injection) was

bioequivalent to the subcutaneous injection used in the pivotal study, EC 404, nor that it was effective or safe by the intra-muscular route. The arguments presented were based on previous studies of other formulations in which equivalent efficacy and safety by the two routes had been demonstrated. The argument was by analogy with these previous studies, on the assumption that all formulations would have the same absorption properties after intramuscular and subcutaneous infection.

The reference to supporting clinical data was the sponsor's report, "TAP-144-SR-(3M) 11.25 mg/EC005. Randomized, open label, cross-over study of the clinical efficacy, safety and pharmacokinetic profile of the IM and SC administration route of the three month depot formulation of leuprorelin SR inpatients with metastatic prostatic cancer. Final report. June 10, 1997."

However the overview also states "As the proposed new 6M depot formulation involves a release pattern currently different from that of the 1M or 3M depot formulation, pharmacokinetic and pharmacodynamic studies on the new depot with 22.5 mg and 30 mg leuprorelin acetate were evaluated in the EC 403 study……". The difference in formulation was described in the clinical summary as follows : "The extension of sustained release from 3 months to 6 months could be achieved by increasing the mean relative molecular mass of the poly(D,L-lactic acid) from 13000- 18000 of the 3M-microspheres to 19000- 27000 of the new 6M-microcapsules."

The argument rejected

Because the release pattern of the new formulation differed from those used in previous studies, it cannot be assumed that there is pharmacological or therapeutic equivalence of leuprorelin after subcutaneous and intra-muscular injections without the clinical and pharmacological data, however likely that may be.

Addition of a second route of administration by subcutaneous injection to the previously approved route of intramuscular injections for the registered products

As previously stated, no clinical data were available for evaluation. Brief statements based on animal studies and from an unpublished human study, claimed equivalent efficacy and safety for the two routes.

As no data were available for evaluation, and the proposal was not presented as a bibliographic submission, the evaluator could not recommend approval of the proposed addition because of insufficient evidence. There may be animal data available in this application to support the sponsor's request, and the formulations used in those references cited were the same as those for which the proposal was made. The TGA may wish to decide if this request can be accepted.

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 chemistry or biopharmaceutic issues and the quality evaluator recommended approval.

Nonclinical

Whilst local tolerance of Lucrin XL Depot in rabbits was acceptable after IM administration, there was an intense inflammatory response with significant tissue damage and fibrosis up to 8 months after SC administration. No data were submitted for the registered formulations administered SC but it would be reasonable to assume a similar intense inflammatory response.

It was not possible to predict systemic exposure with Lucrin XL IM or SC since adequate comparative pharmacokinetic data of Lucrin XL and the registered formulations were not provided. There were also no data comparing exposure following IM and SC administration of the registered formulations. Systemic exposure to leuprorelin depends on the rate of release from the PLA microspheres at the site of injection. Release kinetics are likely to be different with IM and SC administration.

The evaluator recommended approval provided the clinical data addressed the deficiencies.

Clinical

New Strength SC – Lucrin XL Depot 30 mg

Serum leuprorelin and testosterone concentrations showed considerable variability after Lucrin XL Depot 30 mg in the dose-finding study EC403. There were two peaks in the serum leuprorelin concentration - time curve, at 2 hours and 4 weeks. Leuprorelin concentrations fell below 100 pg/mL by week 20. Serum testosterone concentrations followed serum leuprorelin. No direct comparison was made with the registered Lucrin Depot formulations.

In study EC403 conducted in Germany, patients with prostate cancer were randomised to either a single dose of 22.5 mg (n=31) or 30 mg (n=31) SC of Lucrin Depot XL. The mean±SD age of patients was 71±6 years. The primary efficacy variable was percentage of patients achieving castrate serum testosterone concentration (≤ 1.73 nmol/L) within 12 weeks and maintaining this level to 26 weeks (no more than one consecutive elevation at weekly visits) – referred to as “responders”.

One Lucrin XL Depot 30 mg subject was excluded due to lack of data. In subjects analysed, there was a trend to better response with Lucrin XL Depot 30 mg (80%) than Lucrin XL Depot 22.5 mg (68%). The difference was not statistically significant – 95% CI of difference [-13%, 37%]. The median time to castrate serum testosterone was 14 days with both doses in responders and 21 and 15 days respectively with the 22.5 and 30 mg doses in non-responders.

The pivotal trial EC404, in Germany, Austria and Poland, was a randomised trial of three leuprorelin doses over 12 months in patients with prostate cancer. The first group received Lucrin XL Depot 22.5 mg x 2 (n=118), the second Lucrin XL Depot 30 mg x 2 (n=120) and the third Lucrin Depot 11.25 mg x 4 ((n=58). Lucrin Depot 11.25 mg is the EU registered 3-month formulation. All doses were administered SC. The median age of subjects was 73, range 55-85 years. Subjects were stratified by previous hormone therapy. The primary efficacy variable was response defined as maintenance of castrate serum testosterone concentration (≤ 1.73 nmol/L) over 12 months (or no more than one consecutive elevation at monthly visits).

One Lucrin XL Depot 22.5 mg subject was excluded due to lack of data. In subjects analysed, there was a trend to better response with Lucrin XL Depot 30 mg (93%) than Lucrin XL Depot 22.5 mg (86%) and Lucrin Depot 11.25 mg (81%). The differences amongst groups were not significant.

Stratum A patients (previous hormone therapy) had response rates ≥ 90% with all three doses, whereas Stratum B patients (hormone therapy naïve) had lower response rates (79-91%).

No differences in clinical response (as assessed by digital rectal examination, performance status, EORTC criteria and tumour staging) amongst the three doses were apparent.

The sponsor presented a further analysis in their response of 30 September 2009 to the clinical evaluation showing a marginally statistically significant benefit for Lucrin XL Depot 30 mg over Lucrin XL Depot 22.5 mg (p=0.049 exact) based on percentages of subjects with complete suppression, single point elevation and confirmed elevation of serum testosterone.

All subjects in study EC403 (n=31 in each dose group) were included in the safety population. The median duration of treatment was 6.9 months. The incidences of adverse events overall and serious adverse events were slightly higher with Lucrin XL Depot 30 mg than Lucrin XL Depot 22.5 mg – overall 65% versus 61%, serious 13% versus 10%. Common adverse events (30 mg versus 22.5 mg) were flushing (19% versus 36%), injection site erythema (13% versus 16%), erectile dysfunction (10% each) and injection site induration (10% each). There were no new safety issues.

All subjects in study EC404 (n=120, 118 and 58 for 30 mg, 22.5 mg and 11.25 mg respectively) were also included in the safety population. The median duration of treatment was 11.8 months. The incidences of adverse events overall were similar amongst groups (79%, 83% and 78% for 30 mg, 22.5 mg and 11.25 mg respectively). However, the incidence of serious adverse events was higher in the 30 mg group (16% versus 12% for each of the other groups). Only one serious event (worsening of gynaecomastia) was considered drug-related. Common adverse events (30 mg, 22.5 mg, 11.25 mg) were flushing (34%, 37%, 43%), hypertension (21%, 16%, 14%), hypercholesterolaemia (8%, 13%, 12%) and increased sweating (7%, 8%, 10%). Injection site reactions increased with increasing dose; however, most were mild and none severe. There were no unexpected adverse events.

New Strength IM – Lucrin XL Depot 30 mg

No evaluable data. The sponsor has withdrawn this part of the application.

New Route (SC) – Lucrin Depot 7.5, 22.5, 30 mg

In the sponsor's response to the TGA's clinical evaluation report, three studies were mentioned to support this route: study TAP-144-SR 02 (submitted to TGA in 1988), Mazzei et al 1989 and Bischoff et al 1990.[9,10] These data were not considered satisfactory for the following reasons:

- It was not clear how the data addressed the question. The TAP-144-SR 02 study compared leuprorelin 7.5 mg SC and IM over 4 weeks which is relevant for the 7.5 mg strength but not the other strengths. The Mazzei and Bischoff studies are case series with the majority of subjects receiving leuprorelin 3.75 mg SC every 4 weeks. How can the data be extrapolated to Lucrin Depot 7.5 mg (1-month), 22.5mg (3-month) and 30 mg (4-month) SC?
    - It was not stated if the products used in these studies were the same as the registered products.

[9] Mazzei et al. Pharmacokinetics, endocrine and antitumour effects of leuprolide deport (TAP-144-SR) in advanced prostatic cancer: a dose-response evaluation. Drugs Exptl Res 1989; XV: 373-387.

[10] Bischoff et al. 3.75 and 7.5 mf leuprorelin acetate depot in the treatment of advanced prostatic cancer: preliminary report. J Internat Med Res 1990; 19: 103-113.

- It was not clear if this was an unbiased collection of studies. Submission of literature is subject to the requirements in the TGA Literature-Based Submissions Guideline http://www.tga.gov.au/docs/pdf/litbsubs.pdf. A new route of administration requires a systematic review.
- The study submitted in 1988 (TAP-144-SR 02) was not re-submitted and addressed in the clinical overview and summary in the context of the present application.
    - There was minimal information on safety.

The evaluator recommended rejection of all parts of the application:

- Lucrin XL Depot 30 mg SC on the grounds of inferior risk-benefit to Lucrin XL Depot 22.5 mg.
- Lucrin XL Depot 30 mg IM on the grounds of lack of data and
- Lucrin Depot 7.5, 22.5 and 30 mg SC on the grounds of lack of data.

Risk-Benefit Analysis

The pharmacokinetic data were limited. There was considerable variability in leuprorelin and testosterone concentrations from Lucrin XL Depot 30 mg SC. There was no comparison of leuprorelin exposure from Lucrin XL Depot 30 mg SC and the registered Lucrin Depot products. There was also no comparison of exposure between the registered Lucrin Depot products IM and SC. The non-clinical data were inadequate to assess comparative exposure.

The two efficacy trials EC403 and EC404 did not clearly distinguish between Lucrin XL Depot 22.5 mg and Lucrin XL Depot 30 mg. Statistically, there was a trend in favour of the 30 mg dose in initiation and maintenance of castrate serum testosterone, but the clinical significance of any difference was uncertain. There were no differences in clinical response between groups in the pivotal trial EC404. Also, in the pivotal trial, Stratum A patients (previous hormone therapy) had high response rates (≥ 90%) with all doses and appeared more sensitive to hormone therapy than Stratum B patients (hormone therapy naïve). More work is needed to define the optimum dose and patient population. There was no comparison with an Australian- registered formulation.

Neither trial identified new safety issues although the number of subjects was low. In the larger trial EC404, the incidence of serious adverse events was higher with Lucrin XL Depot 30 mg than Lucrin XL Depot 22.5 mg. Event rates for severe adverse events and injection site reactions were also higher with Lucrin XL Depot 30 mg. The use of event rates rather than incidences makes comparisons difficult. The Delegate accepted the sponsor's arguments that the incidences of these events were not unduly high with Lucrin XL Depot 30 mg.

Overall, the efficacy of the proposed Lucrin XL Depot 30 mg SC was demonstrated and its safety acceptable. Therefore, the Delegate recommended approval.

There were no evaluable data on the efficacy or safety of Lucrin Depot 7.5, 22.5 and 30 mg SC. Coupled with the absence of data on comparative exposure, it is difficult to assess the risk-benefit of these formulations via the new route. Therefore, the Delegate did not recommend approval of Lucrin Depot 7.5, 22.5 and 30 mg SC.

The sponsor agreed with the Delegate's action.

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.

The ACPM recommended approval of the submission from Abbott Australasia Pty Ltd to register the new strength for leuprorelin acetate Lucrin XL Depot 30 mg for subcutaneous administration, for the indication:

for palliative treatment of locally extensive or metastatic prostate cancer (Stage C and D).

The ACPM recommended rejection of the submission to register the subcutaneous route of administration for leuprorelin acetate Lucrin Depot 7.5, 22.5 and 30 mg.

In making this recommendation, the ACPM agreed with the Delegate that the evidence of safety and efficacy had not been sufficiently demonstrated for Lucrin Depot when given by subcutaneous route.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Lucrin XL Depot–6 month containing (leuprorelin acetate 30mg) powder for diluent prefilled dual-chamber syringe for the indication:

For the palliative treatment of metastatic or locally extensive prostatic cancer (Stages C and D).

The data were insufficient to make certain requested changes to the Product Information document for Lucrin Depot/Lucrin Depot 3-Month/ Lucrin Depot-4 Month (leuprorelin acetate) and this component of the application was not approved.

Attachment 1. Product Information

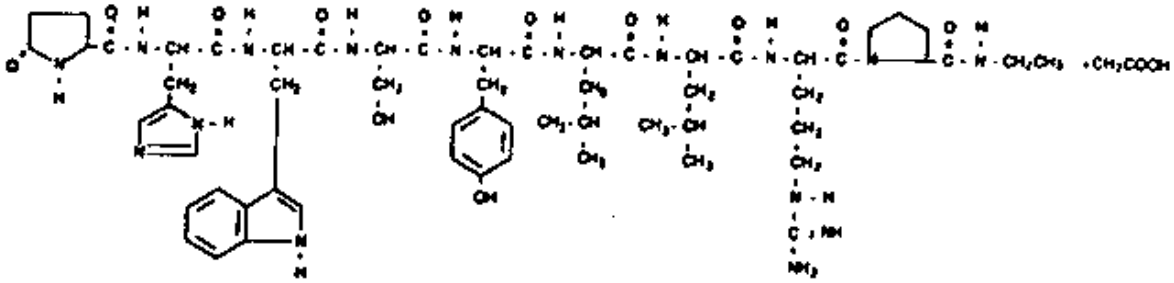
The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION

NAME OF THE MEDICINE

LUCRIN XL DEPOT® PREFILLED DUAL-CHAMBER SYRINGE (PDS) INJECTION
(Sterile leuprorelin acetate for Suspension)

Non-Proprietary Name:
Leuprorelin acetate, Leuprolide Acetate (USAN)



CAS Number: 74381-53-6

DESCRIPTION

Leuprorelin acetate is a synthetic nonapeptide analogue of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH). The analogue possesses greater potency than the natural hormone. Leuprorelin acetate acts as an inhibitor of gonadotropin production and is chemically unrelated to the steroids. The chemical name is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt).

Leuprorelin acetate is a hygroscopic, white or almost white powder. It has a molecular formula of $C_{59}H_{84}N_{16}O_{12}.C_2H_4O_2$ and a molecular weight of 1269.47. The solubility of leuprorelin acetate in water is more than 75% and less than 0.0001% in ether and hexane.

Lucrin XL Depot 6-Month PDS Injection contains leuprorelin acetate (30mg), polylactic acid (270.0mg), and mannitol (52.9mg). The accompanying diluent contains mannitol (50.0.mg), carmellose sodium (5.0mg), polysorbate 80 (1.0mg), water for injections (to 1.0mL) and glacial acetic acid to control pH.

PHARMACOLOGY

Leuprorelin acetate acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Animal and human studies indicate that following an initial stimulation, chronic administration of leuprorelin acetate results in suppression of ovarian and testicular steroidogenesis.

Administration of leuprorelin acetate has resulted in inhibition of the growth of certain hormone-dependent tumours (prostatic tumours in Noble and Dunning male rats and DMBA-induced mammary tumours in female rats) as well as atrophy of the reproductive organs.

In humans, administration of leuprorelin acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males and oestrone and oestradiol in pre-menopausal females). However, continuous administration of leuprorelin acetate results in decreased levels of LH and FSH. In males, androgens are reduced to castrate or pre-pubertal levels. In pre-menopausal females, oestrogens are reduced to post-menopausal levels. These decreases occur within a month of initiating treatment and are maintained as long as treatment continues.

Pharmacokinetics:
Leuprorelin acetate is not active when given orally.

Following a single sc injection of leuprorelin acetate 30mg 6 month depot, serum levels of leuprorelin rise quickly with a subsequent decrease to a plateau within a few days. Within two hours, mean maximum serum levels of 100 ng/mL are measured. In the plateau phase, detectable serum levels were found until up to > 180 days after the last administration.

The mean steady-state volume distribution of leuprorelin following intravenous bolus administration to healthy male volunteers was 27L. In vitro binding to human plasma proteins ranged from 43% to 49%.

In healthy male volunteers, a 1mg bolus of leuprorelin administered intravenously revealed that the mean systemic clearance was 7.6L/h, with a terminal elimination half-life of approximately 3 hours based on a two-compartment model.

The pharmacokinetics of the drug in patients with hepatic and renal impairment have not been determined.

CLINICAL TRIALS

The objective of the pivotal study EC-404 was to investigate the safety and tolerability profile of two 6-month depot dosages administered subcutaneously (22.5mg and 30.0mg leuprorelin acetate, respectively) compared to a 3-month depot (containing 11.25mg leuprorelin acetate – a European registered formulation) over a treatment period of 12 months. The efficacy of the three treatments was also evaluated.

Main inclusion criteria were male patients aged 18 – 85 years with prostate cancer, histologically confirmed by biopsy, of any grade and stage, requiring chemical castration and with a life expectancy of more than 12 months. For patients who had not received prior hormone treatment, testosterone and PSA levels at screening were to be ≥ 5.21nmol/L and ≥1 ug/L respectively (Stratum B) prior to receiving a 1 month depot to ensure hormone sensitivity. Patients receiving GnRH analogue or antiandrogen treatment for < 3 months (Stratum A) and Stratum B patients' testosterone level was to be <2.78 nmol/L prior to randomisation.

The overall response to treatment was defined as successful maintenance of suppressed testosterone serum levels without two consecutive elevations of testosterone levels >1.74 nmol/L after the first injection of the study medication until the end of the observational period at 12 months. Serum levels of testosterone, LH, FSH, PSA and leuprorelin were monitored over the course of the treatment. No differences in clinical response (as assessed by digital rectal examination, performance status, EORTC criteria or tumour staging) amongst the three doses were apparent. One Lucrin Depot 22.5mg subject was excluded due to lack of data.

Response to Treatment (Modified ITT Population)

Stratum	**Treatment**	**Responder**						**Non-Responder**		**Total**	
		<= 1.74 nmol/L		**Single Point Elevation**		**TOTAL (responder)**		**Confirmed Elevation**			
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Stratum A	3M depot 11.25 (n=10)	9	90.0	0	0.0	9	90.0	1	10.0	10	100.0
	6M depot 22.5 (n=23)	17	73.9	4	17.4	21	91.3	2	8.7	23	100.0
	6M depot 30 (n=28)	26	92.9	1	3.6	27	96.4	1	3.6	28	100.0
Stratum B	3M depot 11.25 (n=48)	37	77.1	1	2.1	38	79.2	10	20.8	48	100.0
	6M depot 22.5 (n=94)	69	73.4	10	10.6	79	84.0	15	16.0	94	100.0
	6M depot 30 (n=92)	75	81.5	9	9.8	84	91.3	8	8.7	92	100.0
Total	3M depot 11.25 (n=58)	46	79.3	1	1.7	47	81.0	11	19.0	58	100.0
	6M depot 22.5 (n=117)	86	73.5	14	12.0	100	85.5	17	14.5	117	100.0
	6M depot 30 (n=120)	101	84.2	10	8.3	111	92.5	9	7.5	120	100.0

INDICATIONS

Lucrin XL Depot 6-month PDS Injection is indicated in the palliative treatment of metastatic or locally extensive prostatic cancer (Stage C and D).

CONTRAINDICATIONS

Use in Pregnancy (Category D): Although not relevant to the approved indication, leuprorelin acetate is contraindicated in pregnancy due to its embryotoxic effects.

Use in Lactation: Although not relevant to the approved indication, Lucrin XL Depot® PDS Injection should not be administered to a nursing mother, as it is not known whether leuprorelin acetate is excreted into human milk.

Lucrin XL Depot® PDS Injection is contraindicated in patients with known hypersensitivity to leuprorelin acetate or similar nonapeptides or any of the excipients. Isolated cases of anaphylaxis have been reported with the monthly formulation of Lucrin Depot® 7.5 mg Injection.

PRECAUTIONS

Initially, Lucrin XL Depot® PDS injection, like other LH-RH agonists, causes increases in serum levels of testosterone to approximately 50% above baseline during the first week of treatment. Transient worsening of symptoms, or the occurrence of additional signs and symptoms of prostate cancer may occasionally develop during the first few weeks of Lucrin XL Depot® treatment. A small number of patients may experience a temporary increase in bone pain, which can be managed symptomatically. As with other LH-RH agonists, isolated cases of ureteral obstruction and spinal cord compression have been observed, which may contribute to paralysis with or without fatal complications.

For patients at risk, the physician may consider initiating therapy with daily Lucrin (leuprorelin acetate) injection for the first two weeks to facilitate withdrawal of treatment if that is considered necessary.

Initiating therapy with a non-steroidal anti-androgen at the same time as leuprorelin acetate therapy has proven benefit in reducing flare reactions in 'at risk' patients (eg those with thecal indentation, or at risk of cord compression, and patients with bladder neck obstruction).

Patients with metastatic vertebral lesions and/or with urinary tract obstructions should be closely observed during the first few weeks of therapy.

Bone mineral density changes can occur during any hypo-oestrogenic state. Bone mineral density loss may be reversible after withdrawal of leuprorelin acetate.

Convulsions

Postmarketing reports of convulsions have been observed in patients on leuprorelin acetate therapy. These included patients in the female and pediatric populations, patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and in patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above.

Effects on Fertility:
Clinical and pharmacological studies in adults with leuprorelin acetate and similar analogues have shown full reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks.

Paediatric Use:
Safety and effectiveness in children have not been established.

Carcinogenicity:
A two-year carcinogenicity study was conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). This study also revealed an increased incidence of pancreatic islet cell adenomas, but their incidence showed a negative trend with dose, suggesting that it may not be drug-related. In mice, no pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. In short term toxicity studies in mice treated for 3 months with 20-200 mg/kg, hypertrophic and castration cells were found in the anterior pituitary. Neither pituitary nor pancreatic changes were found in cynomolgus monkeys treated for 12 months with 10 mg/kg daily.

Genotoxicity
Genotoxicity studies have been performed with leuprorelin acetate using bacterial and mammalian systems. These studies provided no evidence of a genotoxic potential.

Interactions with Other Medicines:
No pharmacokinetic-based drug-drug interaction studies have been conducted with Lucrin XL Depot® PDS Injection. However, because leuprorelin acetate is a peptide that is primarily degraded by peptidase and the drug is only about 46% bound to plasma proteins, drug interactions would not be expected to occur.

Laboratory Tests:
Response to leuprorelin acetate therapy may be monitored by measuring serum levels of testosterone, as well as prostate-specific antigen and acid phosphatase. In the majority of non-orchiectomized patients, testosterone levels increased during the first week of treatment. They then decreased and by day 14 had returned to baseline levels or below. Castrate levels were reached in 2 to 4 weeks. Once achieved, castrate levels were maintained as long as the patient received their injections. Transient increases in acid phosphatase levels may occur early in the treatment period; however, by the fourth week the elevated levels usually decreased to values at or near normal. Due to the suppression of the pituitary-gonadal system by Lucrin XL Depot®, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and for up to three months after discontinuation of Lucrin XL Depot® may be affected.

ADVERSE EFFECTS

Side effects seen with Lucrin XL Depot® are due to specific pharmacological action; namely, increases and decreases in certain hormone levels.

In the majority of patients testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment.

'Flare' Phenomenon: The initial increase in circulating levels of pituitary gonadotropins and gonadal steroids leads in some patients to a transient exacerbation of symptoms and signs ('flare' phenomenon). The exacerbation may include worsened bone pain, ureteric obstruction and spinal cord compression. This possibility should be taken into account in deciding to initiate leuprorelin acetate therapy in patients with existing obstructive uropathy or vertebral metastases. Early symptoms of spinal cord compression such as paraesthesia should alert the physician to the need for intensive monitoring and possible treatment.

There is no information available on the clinical effects of interrupting leuprorelin acetate therapy with whether this will produce a withdrawal 'flare'.
Initiating therapy with a non-steroidal anti-androgen at the same time as leuprorelin acetate therapy has proven benefit in reducing flare reactions in 'at risk' patients.

The following table presents the adverse drug reactions (ADR) and frequencies (very common (≥1/10);
common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100) not known (unable to estimate frequency based upon available data) from Lucrin XL 6-Month 30mg clinical studies EC-403 and EC-404 (n=151)

System Organ Class	Preferred Term	Frequency
Blood and lymphatic system disorder	Anaemia	Common
Metabolism and nutrition disorders	Increased appetite	Common
	Abnormal weight gain	Uncommon
Psychiatric disorders	Libido decreased	Common
	Sleep Disorder	Uncommon
Nervous system disorders	Headache	Uncommon
Ear and labyrinth disorders	Vertigo	Uncommon
Cardiac disorders	Heart failure	Common
Vascular disorders	Flushing	Very common
Respiratory, thoracic and mediastinal disorders	Acute pulmonary oedema	Common
Gastrointestinal disorders	Nausea	Uncommon
Skin and subcutaneous tissue disorders	Hyperhidrosis	Common
	Pruritus	Uncommon
	Night sweats	Uncommon
	Hypotrichosis	Uncommon
Renal and urinary disorders	Pollackiuria	Uncommon
	Urinary retention	Uncommon
Reproductive and breast disorders	Erectile dysfunction	Common
	Testicular atrophy	Common
	Testicular pain	Uncommon
General disorders and administration site conditions	Peripheral oedema	Uncommon
	Fatigue	Common
	Injection site reaction	Common
	Injection site inflammation	Common

System Organ Class	Preferred Term	Frequency
	Injection site pain	Common
	Injection site induration	Common
	Injection site erythema	Very common
	Injection site abscess	Common
	Injection site swelling	Common
Investigations	Liver function test abnormal	Uncommon
	Transaminase increased	Common

In clinical trials and postmarketing surveillance, the following adverse events have been observed with this or other formulations of leuprorelin acetate. As leuprorelin has multiple indications and therefore patient populations, some of these adverse events may not be applicable to every patient. For a majority of these adverse events, a cause and effect relationship has not been established.

- ***Body as a Whole***

infection/inflammation, abdomen enlarged, asthenia, chills, fever, general pain, headache, photosensitivity reactions, swelling (temporal bone), jaundice

- ***Cardiovascular System***

congestive heart failure, ECG changes/ischaemia, hypertension, hypotension, myocardial infarction, murmur, phlebitis/thrombosis, pulmonary emboli, transient ischaemic attack/stroke, angina, bradycardia, cardiac arrhythmia, varicose veins, tachycardia.

- ***Digestive System***

constipation, dysphagia, gastrointestinal bleeding, gastrointestinal disturbance, hepatic dysfunction, peptic ulcer, rectal polyps, diarrhoea, dry mouth, duodenal ulcer, increased appetite, liver function tests abnormal, nausea, thirst, vomiting

- ***Endocrine***

diabetes, thyroid enlargement

- ***Metabolic and Nutritional System***

BUN increased, calcium increased, creatinine increased, dehydration, oedema, hyperlipidemia (total cholesterol, LDL - cholesterol, triglycerides), hyperphosphatemia, hypoglycaemia, hypoproteinemia, potassium decreased, uric acid increased, bilirubin increased

- ***Haemic and Lymphatic System***

anaemia, decreased WBC, ecchymosis, lymphedema, PT increased, PTT increased, platelets decreased, increased WBC

- ***Musculoskeletal System***

ankylosing spondylosis, joint pain, pelvic fibrosis, tenosynovitis-like symptoms, joint disorders, myalgia, spinal fracture, paralysis

- ***Nervous System***

anxiety, convulsion, dizziness/light-headiness, headache, hearing disorder, sleep disorders, lethargy, memory disorder, mood swings, nervousness, numbness, peripheral neuropathy,

depression, delusion, hypasthenia, hypoesthesia, insomnia, libido increase, neuromuscular disorders, paresthesia, syncope/blackouts

- ***Respiratory System***

cough, pleural rub, pneumonia, pulmonary fibrosis, pulmonary infiltrate, respiratory disorders, sinus congestion, dyspnea, epistaxis, hemoptysis, pharyngitis, pleural effusion

- ***Skin and Appendages***

carcinoma of skin/ear, dry skin, hair loss, pigmentation, skin lesions, dermatitis, hair growth, hard nodule in throat, pruritus, rash, urticaria, itching

- ***Urogenital System***

bladder spasms, incontinence, penile swelling, prostate pain, urinary obstruction, urinary tract infection, breast pain, breast tenderness, gynecomastia, hematuria, menstrual disorders including breakthrough and sustained vaginal bleeding, penile disorders, testicular atrophy, testicular pain, testicular size decrease, urinary disorders, urinary frequency, urinary urgency

- ***Special Senses***

ophthalmologic disorders, abnormal vision, amblyopia, blurred vision, dry eyes, hearing disorders, taste disorders, tinnitus

Injection site reactions including pain, infection, inflammation, sterile abscess, induration and hematoma have been reported.

There have been very rare reports of suicidal ideation and attempt.

As with other agents in this class, very rare cases of pituitary apoplexy have been reported following initial administration in patients with pituitary adenoma.

Isolated cases of anaphylaxis have been reported.

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 an LH-RH agonist analog. In a clinical trial, 25 men with prostate cancer, 12 of whom had been treated previously with leuprorelin acetate for at least six months, underwent bone density studies as a result of pain. The leuprolide-treated group had lower bone density scores than the non-treated control group. It can be anticipated that long periods of medical castration in men will have effects on bone density.

DOSAGE AND ADMINISTRATION

Lucrin XL Depot® 6-Month Prefilled Dual-Chamber Syringe (PDS) Injection is administered as a single subcutaneous injection **every six months**

- ***LUCRIN XL 6-Month PREFILLED DUAL-CHAMBER SYRINGE (PDS) INJECTION***

For optimal performance of the prefilled dual-chamber syringe (PDS) read and follow the following instructions:

1. To prepare for injection screw the white plunger into the end stopper until the stopper begins to turn.

2. Hold the syringe UPRIGHT. Release the diluent by SLOWLY PUSHING (6-8 seconds) the plunger until the first stopper is at the blue line in the middle of the barrel.

3. Keep the syringe UPRIGHT. Gently mix the microspheres (particles) thoroughly to form a uniform suspension. The suspension will appear milky.

4. Hold the syringe UPRIGHT. With the opposite hand pull the needle cap upward without twisting.

5. Keep the syringe UPRIGHT. Advance the plunger to expel the air from the syringe.

6. Inject the entire contents of the syringe intramuscularly at the time of the reconstitution. The suspension settles very quickly following reconstitution; therefore, leuprorelin acetate should be mixed and used immediately. Re-shake the suspension if settling occurs.

NOTE: Aspirated blood would be visible just below the luer lock connection if the blood vessel is accidentally penetrated. If present, blood can be seen through the transparent hub of the needle.

Although the solution has been shown to be stable for 24 hours following reconstitution, the suspension should be discarded if not used immediately, as the product does not contain a preservative.

As with other drugs administered by injection, the injection site should be varied periodically.

Product contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

OVERDOSAGE

In rats, subcutaneous administration of 250 to 500 times the recommended human dose expressed on a per bodyweight basis, results in dyspnoea, decreased activity and local irritation at the injection site. There is no evidence at present that there is a clinical counterpart of this phenomenon. In early clinical trials with daily subcutaneous leuprorelin acetate in patients with prostate cancer, doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1-mg/day dose.

For advice on the management of overdose please contact the Poisons Information Centre. In Australia please call 13 11 26.

PRESENTATION AND STORAGE CONDITIONS

Lucrin XL Depot® 6-Month Prefilled Dual-Chamber Syringe (PDS) Injection is available in a single dose procedure pack of a dual chamber syringe containing sterile lyophilised microspheres of leuprorelin acetate in the front chamber and 1mL of diluent in the rear chamber.

Lucrin XL Depot® 6-Month PDS Injection may be stored in a cool dry place where the room temperature stays below 25°C. Protect from light.

NAME AND ADDRESS OF SPONSOR

Abbott Australasia Pty Ltd
Sir Joseph Banks Corporate Park
32 – 34 Lord Street
Botany NSW 2019
Australia

POISON SCHEDULE

S4 - Prescription Only Medicine

DATE OF APPROVAL

Date of TGA Approval:
Lucrin XL Depot® 6-Month PDS Injection: xxxxxxxxxxx

Version 01

Therapeutic Goods Administration

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