CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Lucrin PDS Depot 6 maanden 30 mg, powder and solvent for suspension for injection Abbott B.V., the Netherlands

leuprorelin (as acetate)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.
It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 100696

19 April 2011

Pharmacotherapeutic group:	gonadotropin releasing hormone analogues
ATC code:	L02AE02
Route of administration:	subcutaneous
Therapeutic indication:	locally advanced or metastatic prostate carcinoma, in which suppression of the testosterone production to castrate levels is required
Prescription status:	prescription only
Date of authorisation in NL:	6 March 2009
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Lucrin PDS Depot 6 maanden 30 mg, powder and solvent for suspension for injection from Abbott B.V. The date of authorisation was on 6 March 2009 in the Netherlands.

The product is indicated for treatment of locally advanced or metastatic prostate carcinoma, in which suppression of the testosterone production to castrate levels is required. The indication approved in the initial application was 'treatment of metastatic prostate carcinoma, in which suppression of the testosterone production to castrate levels is required.' The indication has been extended to include treatment of locally advanced prostate carcinoma through a type II variation, which is discussed in Annex I of this PAR. A comprehensive description of the indications and posology is given in the SPC.

Leuprorelin is a synthetic nonapeptide analogue of naturally occurring gonadotrophin releasing hormone (GnRH), which possesses greater potency than the natural hormone. Leuprorelin acetate is a peptide and therefore unrelated to the steroids. Chronic administration results in an inhibition of gonadotrophin production and subsequent suppression of ovarian and testicular steroid secretion. This effect is reversible on discontinuation of therapy.

Administration of leuprorelin results in an initial increase in circulating levels of gonadotrophins, which leads to a transient increase in gonadal steroid levels in both men and women. Continued administration of leuprorelin acetate results in a decrease of gonadotrophin and sex steroid levels. In men serum testosterone levels, initially raised in response to early luteinising hormone (LH) release, fall to castrate levels of 0.5 ng/ml, in about 3-4 weeks.

This national procedure concerns a line extension to Lucrin PDS Depot 3.75 mg and 11.25 mg powder and solvent for suspension for injection (NL Licence RVG 30197-30198), which have been registered by the same MAH since 11 November 2004. The 3.75 mg strength is a 1-month prolonged-release formulation and the 11.25 mg strength is a 3-month prolonged-release formulation. With this application an additional strength is introduced: a 30 mg product for prolonged release over a 6-month period.
Ultimately, reference is made tot the first Lucrin product registered in the Netherlands, Lucrin solution for injection 5 mg/ml (NL License RVG 11645) which was authorised on 1 March 1989.

This national procedure concerns a so-called full dossier application according to Article 8(3) of Directive 2001/83/EC, a dossier with administrative, chemical-pharmaceutical, pre-clinial and clinical data.
The active component of Lucrin PDS Depot 6 maanden 30 mg is considered to be well-known and the clinical pharmacology of leuprorelin has been extensively studied. Parts of the data in the dossier of Lucrin PDS Depot 6 maanden 30 mg were already submitted in the dossiers of Lucrin solution for injection 5 mg/ml (NL License RVG 11645) and Lucrin PDS Depot 3.75 mg and 11.25 mg (NL License RVG 30197-30198).

An overview is provided on the pharmacology, pharmacology and toxicology of leuprorelin in the 1-, 3- and 6-month release formulation.
The clinical documentation consists of two clinical studies: one pharmacokinetic/pharmacodynamic study (EC 403) and one study on safety and tolerability (EC 404).

No scientific advice has been given to the MAH with respect to these products. No paediatric development programme has been submitted, as this is not required for a line extension.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is leuprorelin acetate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The drug substance is a white or almost white hygroscopic powder, which is soluble in water and glacial acetic acid and insoluble in ether and hexane.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the CEP and the Ph.Eur. The analytical methods also comply with the Ph.Eur. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Lucrin PDS Depot 6 maanden 30 mg consists of a white lyophilised powder and a colourless solvent. It contains 30 mg leuprorelin acetate in the form of sterile lyophilised microparticles. After reconstitution the solution has a pH of 5-7 and osmolarity of 650 mOsm.

The powder is packed in a prefilled dual-chamber syringe. The front chamber contains the drug substance in prolonged-release microspheres. The rear chamber contains 1.0 ml of a vehicle for suspension of the microspheres. The vehicle is the same as the approved solvent for Lucrin PDS Depot 11.25 mg

The excipients are:
Powder- polylactic acid, mannitol (E421)
Solvent - croscarmellose sodium (E466), mannitol (E421), polysorbate 80 (E433), glacial acetic acid (for pH adjustment) and water for injections.

The composition of the drug product at issue is almost dose-proportional compared with the 11.25 mg strength and packaged in the same syringe.

Pharmaceutical development

In general the development of the product is satisfactory performed and explained. No problems with irritation at the site of injection have been observed during the clinical trials. The excipients used are common in the manufacture of this pharmaceutical dosage form. The registered product Lucrin PDS depot 11.25 mg has the same qualitative composition.

During the formulation development microspheres containing PLA of varying molecular weights were manufactured. The release profiles of the drug substance from the microspheres were evaluated. Information was included on an *in-vivo* study in rats. Furthermore a release profile for the drug product determined in rats is included. It can be seen that almost 100% of the drug is released in 28 weeks, whereas the release remains constant over 26 weeks.

An overage of polysorbate 80 is applied for this formulation. The MAH sufficiently justified this overage, which is also applied for the already approved 3.75 and 11.25 mg strengths. The overage is applied to meet the requirements for extractable volume of the Ph.Eur. monograph 'Parenteral preparations'. The batches used in the clinical studies are manufactured according to the approved process.

The pharmaceutical development of the product has been described in sufficient detail.

Manufacturing process

The powder and solvent for suspension for injection are manufactured under aseptic conditions. To manufacture the microsphere powder, the drug substance and excipients are dissolved and filtered. The solutions are mixed to form an emulsion, out of which microspheres are formed.

The solvent is prepared by mixing of the excipients and filling into the syringe, which is then sterilized. After sterilization the microsphere powder is also filled into the syringe. Sufficient details are provided. The critical steps have been adequately investigated. Adequate in-process controls have been laid down.

Process validation data have been included for three batches from each manufacturing site, sufficiently justifying the maximum batch scale.

Control of excipients

Except for polylactic acid, the excipients comply with the Ph.Eur. The specifications are acceptable.

Container closure system

The prefilled dual-chamber syringe consists of a front assembly, glass cartridge, rubber stoppers, a finger grip and plunger rod. The 23 gauge needle is acceptable in view of the microspheres. The extractables from rubber stopper to the vehicle for the 11.25 mg strength were investigated. No increase in extractables is seen after three months of storage at accelerated storage conditions.

The glass cartridge of the container closure system is siliconized as are the rubber stoppers. Results of the silicone concentration in the vehicle for Lucrin PDS Depot 11.25 mg are included. Since the 11.25 mg strength and the drug product at issue are packaged in the same syringe and comparable compositions, the submission of the results for the 11.25 mg strength is acceptable.

The MAH has investigated the deliverable volume of the prefilled syringes.

Quality control of drug product

The product specification for the powder and solvent for suspension for injection includes tests for appearance, identity, assay, pH, needle passability, bacterial endotoxins, external sterility, drug release, water content and uniformity of content and foreign insoluble matter, extractable volume and sterility.

The release and shelf life requirements are acceptable. The analytical methods have been adequately described and validated. Batch analyses results for at least three production-scale batches of each manufacturing site. Compliance with the release requirements is demonstrated.

Stability of drug product

Three batches of drug product in the prefilled dual-chamber syringe and three batches of the microsphere powder in vials have been stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). One batch of the vials has also been stored inverted. No changes are observed.

Results of forced degradation studies show that the analytical method is sufficiently stability indicating. A photostability study shows that the drug product is stable with respect to light.

The reconstituted product has been stored at 25ºC for 24 hours. Except for a small increase in released leuprorelin, no changes are observed. Based on the stability data provided, the claimed shelf life of 36 months is justified without special storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

The non-clinical documentation consists of non-clinical written and tabulated summaries on the pharmacology, pharmacology and toxicology of leuprorelin in the 1- and 3-month release formulation. No separate non-clinical overview has been provided.

Good Laboratory Practice
The MEB has been assured that the non-clinical studies have been conducted in accordance with acceptable standards of Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Pharmacokinetics
The release of leuprorelin from Lucrin PDS Depot 30 mg has been investigated in male rats after the administration of a 9 mg single subcutaneous dose of leuprorelin acetate. A pilot and a clinical batch have been tested. The results showed that leuprorelin is slowly removed from the site of injection leading to steady concentrations of leuprorelin in serum. These concentrations were pharmacologically active as shown by satisfactory testosterone suppression for the required 6-month period. It is, however, not clear whether these findings can be extrapolated to human, since the proposed therapeutic dose per 6 months of 30 mg (5 mg/kg for a 60 kg person) is lower than the dose used in the rat study of (40 mg/kg). This point should be addressed clinically.

Toxicology
For Lucrin PDS Depot 30 mg no separate non-clinical overview has been provided. The MAH referred to the available non-clinical data from Lucrin PDS Depot 3.75 mg and Lucrin PDS Depot 11.25 mg. None of the available toxicity data indicate any potential toxicological hazard to humans. In addition, the results of mutagenicity studies such as reversion tests, chromosomal aberration tests and micronucleus tests were negative. An ERA is not required, since it is not expected that a significant increase in use of leuprorelin will result from the introduction Lucrin PDS Depot 30 mg.

Local tolerance
The local tolerance of proposed 6 month formulation of Lucrin PDS Depot 30 mg was examined in rabbits after a single subcutaneous or intramuscular injection. At the sites of administration, slight irritant effects were subcutaneously and intramuscularly observed in the tested dose range of up to 45 mg/2 ml per site. These effects consisted of a foreign body reaction, which were most likely related to the removal of poly(D,L-lactic acid) polymer microspheres. These lesions were alleviated from 26 weeks after dosing but were not completely resolved at the end of the study (34 weeks). This is not a concern, since poly(D,L-lactic acid) is biodegradable polymer and because of the small size of the microspheres, which are easily removed by cellular activity. Therefore, Lucrin PDS Depot 30 mg is considered to be safe in clinical use, despite the somewhat higher concentration therapeutic dose of 30 mg/ml per site.

Environmental risk assessment
The drug substance, leuprorelin acetate is not a new active substance or live vaccine. Products containing leuprorelin acetate as drug substance have been authorised in the EU for more than 25 years. In this case the possible risks for the environment arising from use, storage and disposal of the medicinal product are covered by the instructions/measures that are included in the Patient Information Leaflet.

II.3 Clinical aspects

In support of the application for Lucrin PDS Depot 6 maanden 30 mg as a line extension to the approved products Lucrin® 3.75 mg and 11.75 mg Depot, data were provided on two clinical studies: EC 403 and EC 404. Both were pharmacokinetic/pharmacodynamic studies; the former is also an efficacy study, the latter focused primarily on tolerability and safety. The results of these studies are discussed below.

Quality of clinical studies, compliance with GCP

The MEB has been assured that GCP standards were followed in an appropriate manner in the studies conducted. The studies were performed in accordance with the ICH guideline for GCP (CPMP/ICH/135/95), the ethical principles of the Declaration of Helsinki and the requirements of the German Drug Law (Arzneimittelgesetz, AMG).
The formulation of the batches used in key clinical studies is equivalent to that proposed for marketing.

Clinical Pharmacokinetics

Study EC 403

Design

Study EC 403 was a pharmacokinetic/pharmacodynamic single shot injection study comparing two 6 months depots with 22.5 and 30 mg (both arms 31 subjects, mean age 70 years). This was a randomised, open label, multicenter, parallel group phase II/III study in histologically confirmed prostate cancer.
The primary objective was achievement of testosterone values below castration level within 12 weeks until week 26 and continuous release of leuprorelin from depots over 26 weeks. Secondary criteria were LH and FSH suppression within 12 weeks until week 26 and PSA suppression as surrogate parameter of tumour progression, clinical remission/progression and safety.
Each group (22.5 and 30 mg) was planned to include 24 evaluable subjects. Responders were patients without two consecutive elevations of testosterone > 50 ng/dl.

Results

Non-compartmental methods were used to calculate the pharmacokinetic parameters of leuprorelin, and C_{max}, t_{max}, $AUC_{(0\text{-}tlast)}$, $AUC_{(0\text{-}26)}$, and $AUC_{(0\text{-}30)}$ were computed based on actual blood sampling times for responders and non-responders. A summary of the pharmacokinetic parameters for responders and non-responders is given in Table 1, and mean serum-concentration-time curves are provided in Figure 1.

Serum leuprorelin concentrations vs. time curves showed a similar course in both the 6M 22.5 mg group and the 6M 30 mg group for responders, with not-significant differences between concentrations obtained in the 22.5 and 30 mg group. At about 2 hours after leuprorelin administration, the first maximum concentration in responders was reached (88.557 ± 22.767 pg/mL in the 22.5 mg group and 98.396 pg/mL ± 29.463 pg/mL in the 30 mg group), followed by an exponential decrease leading to minimum leuprorelin levels at visit 5 (week 1). Thereafter a small second peak was seen at week 8 in the 22.5 mg group and at week 4 in the 30 mg group. Serum leuprorelin concentrations vs. time curves showed a similar course in both the 6M 22.5 mg group and the 6M 30 mg group for non-responders.

Table 1. Pharmacokinetic serum leuprorelin parameters for responders and non-responders (Study EC 403)

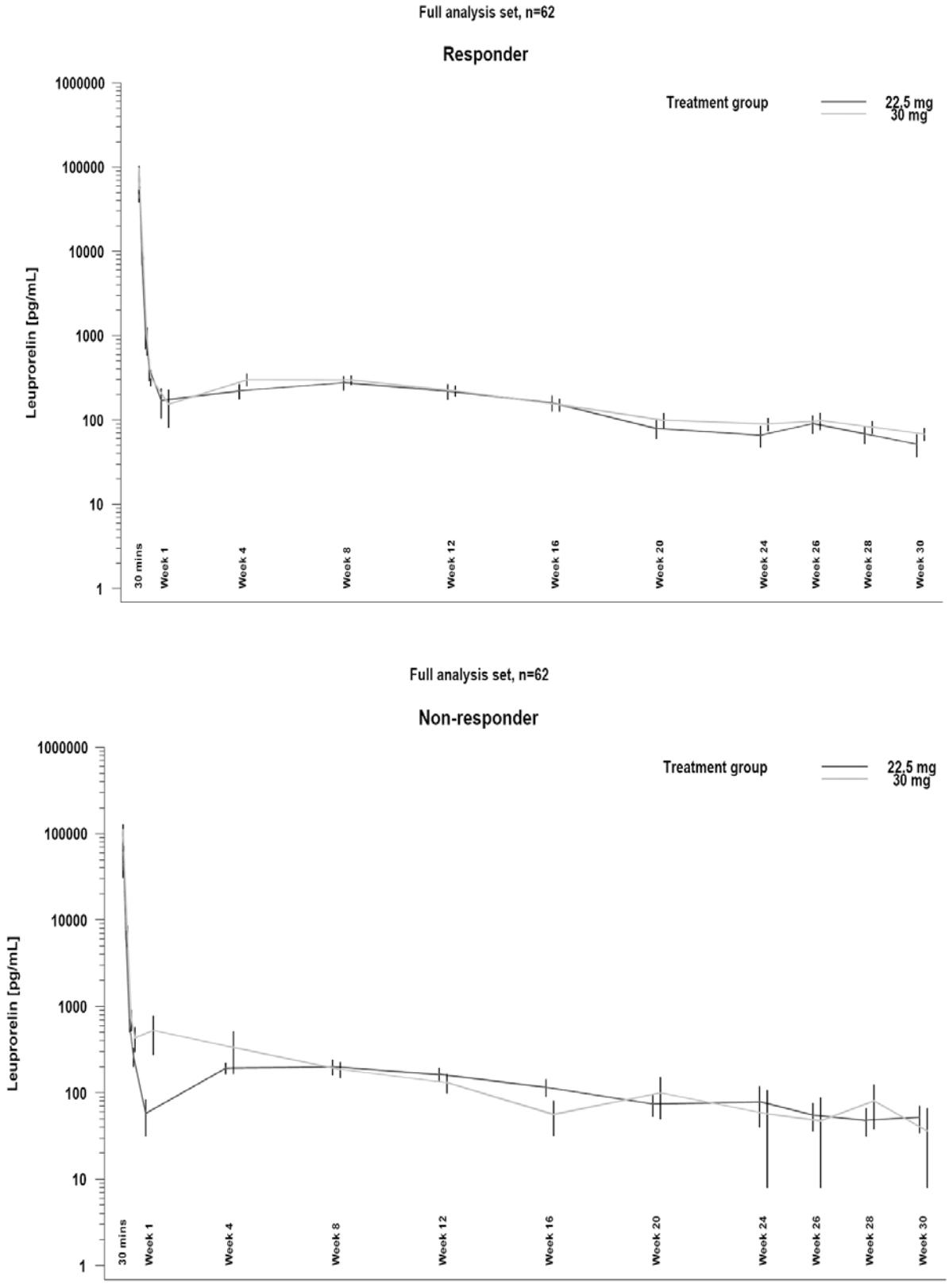
Responders

	Treatment group 22.5 mg					Treatment group 30 mg				
	Arith. mean	SD	Geo. mean	Median	N	Arith. mean	SD	Geo. mean	Median	N
$c_{(max)}$ [pg/mL]	88557	22767	85970	87935	21	98396	29463	93664	94409	23
$t_{(max)}$ [hrs]	1.88	0.63	1.79	2.00	21	1.94	0.56	1.87	2.00	23
$AUC_{(0\text{-}tlast)}$ [(pg*hrs)/mL]	1819872	962341	1653317	1626206	21	1992412	766502	1856767	1881087	23
$AUC_{(0\text{-}26)}$ [(pg*hrs)/mL]	1811180	924039	1655560	1596494	20	1937338	729106	1812195	1850641	23
$AUC_{(0\text{-}30)}$ [(pg*hrs)/mL]	1829776	955019	1668417	1626206	21	2001950	779969	1862434	1910426	22

Non-responders

	Treatment group 22.5 mg					Treatment group 30 mg				
	Arith. mean	SD	Geo. mean	Median	N	Arith. mean	SD	Geo. mean	Median	N
$c_{(max)}$ [pg/mL]	73202	19894	71111	63239	10	116340	43834	109117	116149	6
$t_{(max)}$ [hrs]	2.07	1.43	1.78	1.98	10	1.36	0.64	1.21	1.38	6
$AUC_{(0\text{-}tlast)}$ [(pg*hrs)/mL]	1391879	407379	1333954	1427480	10	1950069	839780	1779411	2024459	6
$AUC_{(0\text{-}26)}$ [(pg*hrs)/mL]	1424952	395552	1371339	1433299	8	1684438	545109	1616546	1902323	3
$AUC_{(0\text{-}30)}$ [(pg*hrs)/mL]	1544147	295645	1524095	1466012	8	1715649	574752	1641966	1907699	3

Figure 1. Mean leuprorelin serum level following administration of a single 22.5 or 30 mg leuprorelin dose to patients, for responders and non-responders (Study EC 403).



Clinical Efficacy

Study EC 403

Initial increase of testosterone levels was seen in responders and non-responders, which was followed by a suppression of testosterone. All subjects in the 22.5 mg and 30 mg groups showed decrease in testosterone concentrations to 50 ng/dl within 12 weeks, suppressed testosterone levels maintained in 24 subjects (80%/86% in those who completed the study) until at least week 26 in the 30 mg group compared to 21 subjects (67.7%) in the 22.5 mg group. The difference in rates of responders between the two treatment arms was 12.3% with 95% confidence interval of [-12.8%,37.3%].

All of the patients in the 30 mg group had values of testosterone ≤ 50 ng/dl from week 4 to 22 onwards. In week 23 and 24 the overall suppression rate was still 96.0% (24/25) and 96.0% (24/25) resp. and then dropped in week 25 and 26 to 92.0% (23/25) and 92.3% (24/26) resp.

PSA levels were > 4 ng/dl at study start and by week 20 the majority of responders were in the range below 0.4 ng/dl. This was true for both treatment groups. In the responders group 90.5% (19/21) in the 22.5 and 100% (24/24) in the 30 mg group showed a complete or partial remission by study end judged by EORTC criteria. The balance of evidence indicates that the efficacy rate is in advantage of the 30 mg dose. This is the reason for the MAH to use the 30 mg depot for registration.

Study EC 404

This was a randomised, open-label, multinational, three arm parallel group comparative, phase III study with Lucrin® 3 month depot of 11.25 mg and two dosages of Lucrin® 6 months depot resp. 22.5 and 30 mg. Patients had histologically confirmed prostate cancer that needed hormone ablation.

340 patients were screened and 296 were randomised. 37 patients completed the study in the 11.75 mg arm, 87 in the 22.5 mg depot arm and 89 in the 30 mg depot arm. Safety data of at least 100 patients were prospectively collected for one year, which is according to the guideline concerning submission of long-term treatment (note for guidance on population exposure to assess clinical safety: CHMP/ICH/375/95).

The primary study objective was safety and tolerability of the two six-months depots 22.5 and 30 mg Lucrin® over 12 months compared to the marketed 11.25 mg three-months depot.

The secondary study objectives were testosterone levels ≤ 50 ng/dl from month 1 till month 12, LH, FSH, PSA, clinical outcome and leuprorelin serum levels. Response was defined as suppressed testosterone serum levels without two consecutive elevations of testosterone level > 50 ng/dl after first injection until month 12. A patient that had a testosterone level ≤ 50 ng/dl following an elevation of > 50 ng/dl, was considered a responder. PSA was used as surrogate parameter for detection of progression of prostate carcinoma.

There were two kinds of patients enrolled in this study: those pretreated for up to 3 months with any GnRH analogues with or without anti-androgens and with testosterone levels < 80 ng/dl prior to randomisation (stratum A). The other category (stratum B), were therapy-naïve patients who received one injection of 1 month depot 3.75 mg Lucrin®. For these patients testosterone levels had to be ≥ 150 ng/dl and PSA ≥ 1 ng/ml.

Overall, suppression of testosterone to castration level was 81.0% in 3 the month 11.25 mg group, 85.5% in 6 month 22.5 mg depot group and 92.5% in the 6 months 30 mg depot group for the ITT population (stratum A and B; Table 1). The suppression rate of testosterone for the 30 mg depot was 94% at 6 months and 98% at 12 months (Table 2). Non-responders had lower leuprorelin levels than responders.

There were 10 patients with single point elevations during the treatment course with 30 mg 6 months depot Lucrin® (13 events). From these 13 events 8 had marginal increases of testosterone (below 100 ng/dl) and all had suppressed levels after this single point elevation.

There were no complete remissions. Previous studies from literature show that testosterone suppression improved symptoms and patient survival by several months but was not curative.

Partial remission and objective stabilisation was seen in 93.2%, 94.0% and 85% for the 11.25, 22.5 and 30 mg depots respectively. However, the objective progression rate was higher in the 30 mg depot compared to the other dosages; 3.4% (11.25 mg) and 6% (22.5 mg) versus 11% (30 mg).

The progression rate was resp. 3.4% in 11.25 mg, 6% in 22.5 mg and 11% in 30 mg Lucrin®. It was stated that the higher objective progression rate in the 30 mg treatment arm was due to higher staging

(T4), higher incidence of lymph node involvement (N1) and higher incidence of distance metastases at screening. Overall the tumour staging was indeed higher in the 30 mg Depot group, however no clinically relevant differences between the groups were seen at the end of the study concerning disease progression.

The secondary end points in responders between LH, FSH and PSA levels did not differ significantly, however non-responders showed higher levels of LH, more FSH variations and slight increase of PSA.

Table 1. Response to treatment (ITT population) study EC 404

Stratum	Treatment	Responder						Non-responder		Total	
		≤ 50 ng/dL		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	10.0	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 2. Testosterone suppression rate in EC 404 in patients with 30 mg depot Lucrin®

	Suppression rate with 6 months 30 mg depot Lucrin®
Month 1	95% (114/120)
Month 2	94% (112/119)
Month 3	95% (111/117)
Month 4	94% (109/116)
Month 5	93% (107/115)
Month 6	94% (104/111)
Month 7	98% (100/102)
Month 8	98% (98/100)
Month 9	96% (96/100)
Month 10	97% (96/99)
Month 11	97% (95/98)
Month 12	98% (96/98)

Clinical safety

Overall the safety profile of GnRH agonists is well known. Common adverse events are injection site reaction, headache, flushes, osteoporosis, loss of libido, impotence and weight increase, with hot flushes being the most common adverse event.

Study EC 403

The number of subjects experiencing adverse events was 61.3% in the 22.5 mg depot group and 64.5% in the 30 mg depot group (Table 3-5). Adverse events were higher in the 30 mg group versus 22.5 mg depot group, 10 AEs in 4 subjects versus 5 AEs in 3 subjects. Severe adverse events (Table 4) were seen in 4 subjects (7 AEs in 30 mg depot) versus 2 subjects (2 AEs in 22.5 mg depot). One patient experienced acute pulmonary edema and cardiac failure, possibly an acute allergic reaction to leuprorelin injection, the patient recovered from this event.

Vascular disorders (only flushes) were the most frequently reported AEs; 35% in the 22.5 mg patients versus 19% in the 30 mg patients. This AE is well known and are due to the hormone modulating effect of this drug.

The major adverse events related to study medication reported, were (Table 5): flushing (35.5% in the 22.5 mg and 19.4% in the 30 mg group), injection site erythema (16.1% and 12.9% in the 22.5 and 30 mg group resp.), fatigue (6.5% and 9.7% in 22.5 and 30 mg group resp.), erectile dysfunction (both groups 9.7%), injection site induration (both 9.7%), weight increase (3% and 0% in the 22.5 versus 30 mg group) and pruritus (3% in the 22.5 mg and 0% in the 30 mg group).

In study 403, 2 patients prematurely terminated the study. One due to femur fractures (right and left), wound infection and gastrointestinal hemorrhage. The other patients discontinued the study due to prostate cancer progression, bone metastases progression and intraorbital tumor. No deaths were reported.

No notable changes in laboratory parameters were seen during the EC 403 study, with the exception of haemoglobin concentrations, which showed a decrease in 57.1% (12/21) and 15.8% (3/19) in the 30 mg and 22.5 mg group, respectively. As requested, the MAH provided data concerning baseline values of haemoglobin and values during the study. No statistically significant differences between both treatment arms were observed. The decrease of haemoglobin is of minor clinical relevance. In addition, testosterone suppression itself might induce haemoglobin decrease.

Table 3. Subjects with AEs presented by system organ class (safety population) (EC403)

Subjects with AEs by SOC (a)	Treatment group 22.5 mg N=31	Treatment group 30 mg N=31
	Subjects (%)	Subjects (%)
Any adverse event	19 (61.3%)	20 (64.5%)
Vascular disorders	11 (35.5%)	6 (19.4%)
General disorders and administration site conditions	6 (19.4%)	7 (22.6%)
Infections and infestations	5 (16.1%)	8 (25.8%)
Reproductive system and breast disorders	5 (16.1%)	4 (12.9%)
Renal and urinary disorders	6 (19.4%)	2 (6.5%)
Musculoskeletal and connective tissue disorders	4 (12.9%)	2 (6.5%)
Ear and labyrinth disorders	3 (9.7%)	2 (6.5%)
Injury, poisoning and procedural complications	3 (9.7%)	1 (3.2%)
Nervous system disorders	3 (9.7%)	1 (3.2%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (3.2%)	1 (3.2%)
Skin and subcutaneous tissue disorders	3 (9.7%)	0 (0.0%)
Gastrointestinal disorders	2 (6.5%)	1 (3.2%)
Respiratory, thoracic and mediastinal disorders	1 (3.2%)	2 (6.5%)
Cardiac disorders	0 (0.0%)	2 (6.5%)
Eye disorders	1 (3.2%)	1 (3.2%)
Investigations	1 (3.2%)	1 (3.2%)
Metabolism and nutrition disorders	0 (0.0%)	1 (3.2%)
Psychiatric disorders	0 (0.0%)	1 (3.2%)

Table 4. Overview of adverse events and serious adverse events (safety population) (EC403)

	Treatment group 22.5 mg (n=31)		**Treatment group 30 mg (n=31)**	
	Events (%)	**Subjects (%)**	**Events (%)**	**Subjects (%)**
AEs	71	19 (61%)	57	20 (65%)
related	29		27	
Not-related	42		30	
Mild	39 (55%)		21 (37%)	
moderate	30		29 (51%)	
Severe	2 (3%)		7 (12%)	
Leading to discontinuation	0	0	3	0

SAE	5	3 (10%)	10	4 (13%)
Related	0		2	
Not-related	5		8	
Leading to discontinuation	0	0	3	0
deaths	0	0	0	0

Table 5. Adverse events that occurred in at least 2 subjects during the study and in order of frequency. (EC403)

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%)

Study EC 404

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. Other frequently reported AEs were: general disorders and administration site conditions (19%), infections and infestations (19%),with higher incidences in the 30 mg depot Lucrin® (differences between the treatment arms are summarised in Table 6). The majority of injection site reactions were mild and none was severe.

In study 404 9 patients were withdrawn from the study; 7 deaths (3.4% 11.25 mg, 1.7% 22.5 mg and 4.2% 30 mg; not related to study medication), 1 patient stopped because of headache, vertigo and hyposomnia which was possibly related to study medication and another patient was withdrawn due to bone metastases which were not related to the study drug (Table 7).

Laboratory evaluation revealed no significant changes (including haemoglobin levels).

Overall the frequently reported AEs in both studies (flushing, hypertension, injection site reactions, headache, pruritis and weight increase) are well known side effects of Lucrin®.

Table 6. Adverse events reported in 2% of patients in any treatment group, stratified by system organ class (safety population) (EC404)

SOC decode	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	%
Blood and lymphatic system disorders	2	3.4	3	2.5	12	10.0	17	5.7
Cardiac disorders	5	8.6	10	8.5	13	10.8	28	9.5
Eye disorders	0	--	2	1.7	9	7.5	11	3.7
Gastrointestinal disorders	4	6.9	8	6.8	13	10.8	25	8.4
General disorders and administration site conditions	7	12.1	22	18.6	28	23.3	57	19.3
Hepatobiliary disorders	2	3.4	2	1.7	3	2.5	7	2.4
Infections and infestations	8	13.8	28	23.7	21	17.5	57	19.3
Injury, poisoning and procedural complications	2	3.4	3	2.5	6	5.0	11	3.7
Investigations	4	6.9	8	6.8	9	7.5	21	7.1
Metabolism and nutrition disorders	9	15.5	27	22.9	18	15.0	54	18.2
Musculoskeletal and connective tissue disorders	10	17.2	23	19.5	20	16.7	53	17.9
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	6.9	7	5.9	8	6.7	19	6.4
Nervous system disorders	7	12.1	10	8.5	10	8.3	27	9.1
Psychiatric disorders	3	5.2	8	6.8	7	5.8	18	6.1
Renal and urinary disorders	8	13.8	15	12.7	18	15.0	41	13.9
Reproductive system and breast disorders	1	1.7	6	5.1	6	5.0	13	4.4
Respiratory, thoracic and mediastinal disorders	4	6.9	7	5.9	11	9.2	22	7.4
Skin and subcutaneous tissue disorders	8	13.8	18	15.3	13	10.8	39	13.2
Vascular disorders	31	53.4	56	47.5	56	46.7	143	48.3

Table 7. Main reason for premature study termination (safety population) (EC404)

Main reason	**3 month depot 11.25 mg (n=58)**	**6 month depot 22.5 mg (n=118)**	**6 month depot 30 mg (n=120)**	**Total 296 patients**
	N (%)	N (%)	N (%)	N (%)
Lost to follow-up	0	0	0	0
Adverse events	2 (3.4%)	2 (1.7%)	5 (4.2%)	9 (3.0%)
Lack of efficacy	18 (31%)	29 (24.6%)	21 (17.5%)	68 (23.0%)
Protocol deviation	1 (1.7%)	0	2 (1.7%)	3 (1.0%)
Withdrawal of consent	0	0	3 (2.5%)	3 (1.0%)
Other	0	0	0	0
Total	21 (36.2%)	31 (26.3%)	31 (25.8%)	83 (28%)

Serious adverse events in leuprorelin use described in literature are thromboembolic events and diffuse intravascular coagulation. One report of anaphylaxis shortly after administration of leuprorelin was reported and one patient was described with central retinal vein occlusion with no other risk factors than the leuprorelin administration.

Conclusion on clinical aspects

Overall this new dose of Lucrin Depot was studied in a sufficient population. Following a single SC dose of either 22.5 mg or 30 mg, leuprorelin was detectable in serum after 30 weeks. No accumulation upon multiple dosing was noted.

The efficacy of Lucrin 30 mg was more favourable than the 22.5 mg depot based on:

1. more responders
2. better maintenance of testosterone suppression
3. longer duration of response.

Lucrin 30 mg Depot was able to remain testosteron levels below detection for at least 6 months. The efficacy of Lucrin 30 mg is satisfactory studied and proved. Adverse events of Lucrin are well known.

Although the progression rate was higher in the 30 mg Lucrin depot patients (study 404). This was due to higher staging (T4), higher incidence of lymph node involvement (N1) and higher incidence of distance metastases at screening (M1b). No clinically relevant differences between the groups were seen at the end of the study concerning disease progression. In addition, haemoglobin concentrations decreased far more in the 30 mg than in the 22.5 mg Lucrin (study 403). However, based on all haemoglobin data provided, no statistically significant differences between both treatment arms were observed.

Risk management plan

Leuprorelin was first approved in 1984, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of leuprorelin can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC.

No formal Risk Management Plan or additional risk minimization activities are required beyond those performed as part of regular pharmacovigilance and safety surveillance activities. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the national procedure is in accordance with those accepted for the previously authorised products Lucrin PDS Depot 3.75 mg and 11.25 mg.

Readability test

The package leaflet has not been evaluated via a user consultation study. The MAH will perform user testing once the PILs of various leuproreline authorisations in the EU have been harmonised.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Lucrin PDS Depot 6 maanden 30 mg, powder and solvent for suspension for injection has a proven chemical-pharmaceutical quality and is an approvable line extension to Lucrin PDS Depot 3.75 mg and 11.25 mg powder and solvent for suspension for injection. Lucrin PDS Depot is a well-known medicinal product with an established favourable efficacy and safety profile.

For this application the MAH refers to the registration file of Lucrin solution for injection 5 mg/ml and Lucrin PDS Depot 3.75 mg and 11.25 mg (NL License RVG 11645, 30197-30198). Additionally two clinical studies have been submitted to demonstrate the pharmacokinetic and pharmacodynamic profile, the efficacy and safety of the 30 mg product. The results show successful testosterone suppression, as well as continuous release of leuprorelin from depots over 26 weeks. Overall the frequently reported AEs in both studies are well known side effects of Lucrin. No new safety issues were identified.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other leuprorelin containing products.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Lucrin PDS Depot 6 maanden 30 mg, powder and solvent for suspension for injection was authorised in the Netherlands on 6 March 2009.

The following post-approval commitment has been made during the procedure:

<u>Quality – drug product</u>

- The MAH committed to provide an update of the batch formula for the increased batch size. This commitment has been fulfilled.

List of abbreviations

ADT	Androgen Deprivation Therapy
AE	Adverse Events
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GnRH	Gonadotropin Releasing Hormone
ICH	International Conference of Harmonisation
LHRH	Luteinising Hormone-Releasing Hormone
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
PDS	Prefilled Dual-chamber Syringe
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSA	Prostate-Specific Antigen
PSUR	Periodic Safety Update Report
RT	Radiotherapy
SC	Subcutaneous
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Fulfillment of post-approval commitment.	II	14-4-2009	15-5-2009	Approval	N
Extension of the therapeutic indication to 'Treatment of locally advanced or metastatic prostate carcinoma, in which suppression of the testosterone production to castrate levels is required'.	II	25-6-2009	23-11-2009	Approval	Y, Annex I
Modification of method of administration in SPC and PIL.	II	14-7-2009	2-10-2009	Approval	N
Change in the name of the medicinal product.	IB	17-5-2010	8-7-2010	Approval	N
Change in the address of the MAH.	IA	10-6-2010	3-8-2010	Approval	N
Changes to an existing pharmacovigilance system as described in the detailed description of the pharmaco-vigilance system.	IA	23-6-2010	23-8-2010	Approval	N
Changes to an existing pharmacovigilance system as described in the detailed description of the pharmaco-vigilance system.	IA	23-6-2010	23-8-2010	Approval	N
Changes to an existing pharmacovigilance system as described in the detailed description of the pharmaco-vigilance system.	IA	23-6-2010	26-9-2010	Approval	N
Changes to an existing pharmacovigilance system as described in the detailed description of the pharmaco-vigilance system.	IA	9-9-2010	12-11-2010	Approval	N
PSUR covering the period 13 October 2007 to 3 May 2010	PSUR	1-10-2010	30-11-2010	Approval	N

ANNEX I – Type II variation: Extension of indication

On 25 June 2009 a type II variation was started for extension of the approved indication to *Treatment of locally advanced or metastatic prostate carcinoma, in which suppression of the testosterone production to castrate levels is required.* This concerns all Lucrin formulations (injection fluid (sc, iv) and depot) available in the Netherlands. The overall benefit-risk profile was positive, and therefore the variation was approved on 23 November 2009.

Leuprorelin acetate has an established indication for the palliative treatment of metastatic prostate carcinoma. The data for the treatment of metastatic prostate cancer was fully presented in the original dossier. The focus of this variation is in *non-metastatic disease* in order to widen the indication to treatment of prostate cancer whenever reduction of testosterone levels to castrate values is required, *i.e.* in advanced, both metastatic and non-metastatic prostate carcinoma.

Clinical aspects
In support of the indication for locally advanced prostatic carcinoma, reference is made to:

- Guidelines
- Studies performed with Lucrin
- Overview of studies performed with LHRH agonists in general in non-metastatic disease.

Guidelines
The recommendations of the various guidelines for androgen deprivation therapy (ADT) in locally advanced prostate cancer are summarised in Table 1.

Table 1. Expert guideline recommendations for ADT in locally advanced disease

Guideline	Recommendation
European Association of Urology (2007)	• N+ disease • Locally advanced M0 • Locally advanced symptomatic • Locally advanced asymptomatic unfit for local definitive treatment
European Society of Clinical Oncology (2007)	• Long-term hormone therapy (androgen suppression or bicalutamide monotherapy) is a standard treatment
US National Comprehensive Cancer Network (2007)	• Adjuvant ADT after completion of primary treatment for selected high risk patients treated with radiation therapy • Consideration of immediate ADT in men with positive nodes following radical prostatectomy
American Urological Association (2007)	*Not addressed as guideline relates only to stage T1-T2.*
RCR / BAU (1999)	• Immediate androgen ablation could improve survival for some patients with locally advanced prostate cancer
NICE (Draft) (2007)	*Mentioned only in association with radiotherapy (see*

	section

The recommendations for adjuvant ADT in some or all patients receiving radical local radiotherapy are summarised in Table 2.

Table 2. Expert guideline recommendations for ADT in association with radiotherapy

Guideline	Recommendation
European Association of Urology (2007)	• In locally advanced CaP, overall survival is improved by concomitant and adjuvant hormonal therapy (with a total duration of 2-3 years) with external radiation. • For a subset of patients, T2c-T3 N0-x with Gleason score 2-6, short-term ADT before, and during radiotherapy, may favourably influence overall survival.
European Society of Clinical Oncology (2007)	• Patients receiving external beam radiotherapy should receive androgen suppression with a luteinising hormone-releasing hormone (LHRH) agonist before, during and after radiotherapy for a minimum of 6 months.
US National Comprehensive Cancer Network (2007)	• Giving ADT before, during and/or after radiation prolongs survival in selected radiation managed patients.
American Urological Association (2007)	• For patients in the intermediate risk category, RCTs have shown either short-course hormonal therapy (~ 6 months) and standard-dose external beam radiotherapy or dose escalation should be considered standard. • For patients with locally advanced or high-grade (Gleason score >7), RCTs have shown two to three years of post-radiation adjuvant hormonal therapy to improve survival.
RCR / BAU (1999)	• Neo-adjuvant or adjuvant hormone therapy should be considered for patients with locally advanced (T3-T4) disease who are to be treated with radical radiotherapy.
NICE (Draft) (2007)	• Neo-adjuvant and concurrent luteinising hormone-releasing hormone agonist (LHRHa) therapy for 3 to 6 months is recommended for men receiving radical radiotherapy for high-risk localised or locally advanced prostate cancer. • Adjuvant hormonal therapy for up to 3 years is recommended for men receiving neo-adjuvant hormonal therapy and radical radiotherapy for high-risk localised or locally advanced prostate cancer who have

	a Gleason score of ≥8.

Failure of the serum levels of PSA to fall to undetectable values and/or a subsequent rise following radical prostatectomy or radical radiotherapy is likely to signal either local recurrence or metastasis, even though clinical evidence of these events may not be apparent for months or even years. Expert guidance panels have, therefore, given much consideration to the best ways to deal with this "biochemical relapse". These guidelines are summarised in table 3.

Table 3. Expert guideline recommendations for ADT in biochemical relapse

Guideline	Recommendation
European Association of Urology (2007)	• PSA recurrence indicative of systemic relapse is best treated by early ADT resulting in decreased frequency of clinical metastases. • LHRH analogues/orchidectomy or bicalutamide at 150 mg/day can both be used when there is indication for hormonal therapy.
European Society of Clinical Oncology (2007)	*(Issue not addressed in guideline)*
US National Comprehensive Cancer Network (2007)	• Post radiotherapy (RT) rising PSA → If not a candidate for local therapy → Observation or ADT • Post surgery PSA rising or failure to fall → If lower probability of benefit from RT → RT or ADT
American Urological Association (2007)	*(Not addressed as guideline relates only to initial treatment of stage T1-T2)*
RCR / BAU (1999)	• For the majority of patients, management after PSA failure will either be with a "watch and wait" approach or with immediate hormone therapy.
NICE (Draft) (2007)	Hormonal therapy is not routinely recommended for men with biochemical relapse unless they have: • symptomatic local disease progression; or • any proven metastases; or • a PSA doubling time < 3 months.

Studies performed with Lucrin

Leuprorelin (Lucrin) as an effective inhibitor of testicular testosterone production

Abbou et al (1997) performed a randomised, open, multicentre trial that was conducted in 16 centres in France.

Patients were randomised to receive, every 28 days for 6 months, either subcutaneous injections of leuprorelin 3.75 mg or intramuscular injections of triptorelin 3.75 mg. Both treatment groups also received the anti-androgen nilutamide (300 mg/day) during the first 21 days to prevent flare.

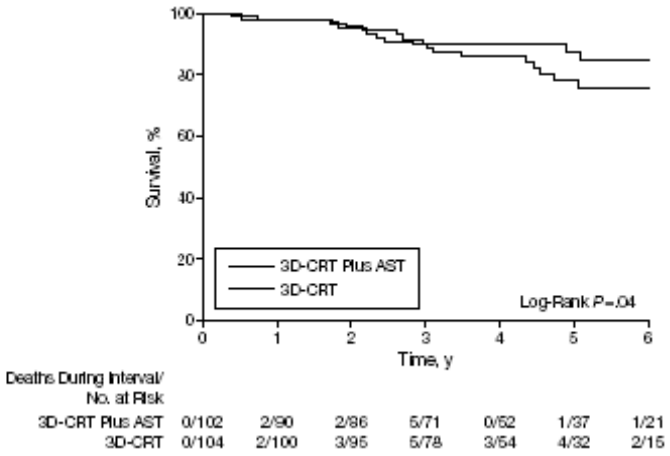
The primary endpoint was the proportion of patients attaining a serum testosterone level ≤0.5 ng/ml, corresponding to the generally accepted castration level.

A total of 68 with confirmed metastatic prostate cancer patients were enrolled and randomised 36 to leuprorelin and 32 to triptorelin. There were no significant differences in demographic or baseline variables between the treatment groups.
In the leuprorelin group 100%, 97% and 100% of patients respectively presented castration levels of testosterone after one, three and six months of treatment. The corresponding percentages for the triptorelin group were 90%, 100% and 96%, the differences between the groups being not statistically significant.

Efficacy in treating non-metastatic prostate cancer

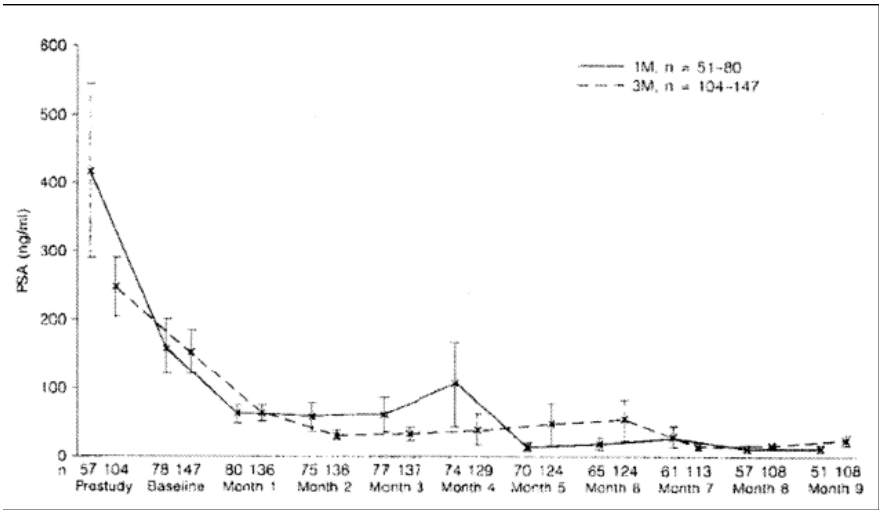
D'Amico et al (2004) conducted a prospective randomised controlled trial of 206 patients with clinically local prostate cancer who were randomised to receive 70 Gy three-dimensional conformal radiotherapy (3D CRT) alone (n=104) or in combination with 6 months of ADT (leuprorelin 7.5 mg per month, n=88 or goserelin 3.6 mg per month, n=10). Eligible patients included those with a PSA of at least 10 ng/ml, a Gleason score of at least 7, or radiographic evidence of extraprostatic disease. In practice, all patients had tumours staged at entry within the range T1b – T2b.
The main outcome measures were time to PSA failure (defined as PSA >10 ng/ml and increasing at a rate of > 0.2 ng/ml on two consecutive visits) and overall survival.
After a median follow-up of 4.52 years, patients randomised to radiotherapy plus ADT had a significantly higher survival (p=0.04), lower prostate cancer-specific mortality (p=0.02) and higher survival free of salvage ADT (p=0.002). Kaplan-Meier estimates (figure 2) of 5-year survival rates were 88% (95% CI: 80-95%) in the combined treatment groups versus 78% (95% CI 68-88%) in the radiotherapy-only group. Rates of survival free of salvage ADT at 5 years were 82% (95% CI: 73-90%) versus 57% (95% CI: 46-69% in the radiotherapy-only group.

Figure 1. **Overall survival for 3D CRT vs. 3D CRT and ADT (D'Amico et al., 2004)**



Wechsel et al (1996) report an open-label Phase II study of leuprorelin in 39 centres in France, Italy, Germany and the UK, the primary purpose of which was to compare the efficacy and safety of 3.75 mg monthly versus 11.25 mg three-monthly. Although both locally advanced and metastatic disease patients were included, patients with stage T3N0M0 (class C) accounted for 114 of the 237 patients recruited (48%).
Mean serum testosterone levels fell below the threshold for chemical castration (0.5 ng/ml) from one month onwards in both treatment groups. The effect of this fall in serum testosterone on the tumour progression was evidenced both by the observed decrease in PSA and the clinical outcome of the patients.

Figure 2. Mean PSA values (n/ml) in patients receiving leuprorelin once a month (1M) and every three months (3M) (intention to treat analysis; Wechsel et al., 1996)



The profile of the decline in serum PSA level mirrored that of serum testosterone in both groups. At the end of the 9-month treatment period, serum PSA levels were reduced to ≤4 ng/ml (the level generally considered to indicate tumour remission) in 65% and 66% of the patients in the monthly and 3-monthly groups respectively. The mean percentage reduction in PSA at the end of the study, compared with pre-treatment baselines, was 93% and 85% in the monthly and 3-monthly groups.
With regard to tumour response to treatment (best response during the course of the study), the results (using EORTC criteria) were:

- Complete remission: 9 patients (4%)
- Partial remission: 82 patients (35%)
- Stable disease: 86 patients (36%).

Bourdin et al (1990) performed an open study in 40 patients with prostate cancers of Jewett-Whitmore classes A2 to C (i.e. non-metastatic) who were treated with leuprorelin 3.75 mg monthly for 2 months before going on to further treatment with pelvic irradiation or radical prostatectomy. Assessment was by rectal examination, and assays for prostatic acid phosphatase, PSA and testosterone.
Of the 32 patients successfully evaluated, 2 (6%) displayed no response, 7 (22%) a minor response and 23 (72%) a major response. Of the 31 patients assayed for PSA both before and after leuprorelin treatment, 26 (84%) had initial PSA concentrations of >5 ng/ml. Concentrations remained high in 6 patients after two months of leuprorelin treatment and 2 of these patients went on to develop bone metastases. Plasma testosterone concentrations fell to <3 ng/ml in 39 patients after 2 months leuprorelin treatment.
It was concluded that clinical response was favourable if initial reversible hormone and transient hormone therapy was given prior to local/regional treatment of prostate cancer. Following radical treatment, there was a high incidence of major responders, with a return of PSA to near normal values. In addition, there was no increase in morbidity if leuprorelin was administered before radical treatment.

Bischoff et al (1990) in Germany treated 190 patients with prostate cancer with leuprorelin 3.75 or 7.5 mg monthly subcutaneously or intramuscularly without concomitant anti-androgen or cytostatic therapy. Eighty-five (44.7%) of these patients had non-metastatic disease.
The two doses and the different routes of administration had similar effects on serum testosterone, dihydrotestosterone, FSH and LH concentration, tumour activity and clinical tolerance.

Table 4. Assessment of remission (Bischoff et al 1990)

Response	1 month n=103	3 months n=101	6 months n=93	9 months n=76	12 months n=61	15 months n=36
Complete remission	0	0	1 (1.1%)	3 (3.9%)	3 (4.9%)	0
Partial remission	14 (13.6%)	27 (26.7%)	39 (41.9%)	32 (42.1%)	21 (34.4%)	12 (33.3%)
Stable disease	80 (77.7%)	62 (61.4%)	45 (48.4%)	32 (42.1%)	31 (50.8%)	18 (50.0%)
Progression	3 (2.9%)	2 (2.0%)	1 (1.1%)	2 (2.6%)	2 (3.3%)	2 (5.6%)
Not available	6 (5.8%)	10 (9.9%)	7 (7.5%0	7 (9.2%)	4 (6.6%)	4 11.1%)

The authors concluded that there were no differences regarding the overall clinical efficacy of the two doses and that leuprorelin offers an important alternative to orchidectomy in the treatment of prostate cancer.

Comparison of normal to depot formulation

Akaza et al (1990) reported a Japanese multicentre study of leuprorelin 3.75 mg or 7.5 mg 4-weekly for up to 16 weeks in 81 evaluable patients with Jewett-Whitmore class B, C, or D prostate cancer. Approximately 40% of the patients had class B or C tumours and hence non-metastatic disease.

Almost all patients showed a reduction in serum testosterone to the castrate level (here defined as 1 ng/ml) within 3-4 weeks. Overall response rates for the primary tumour (across all classes of disease) were:

- Complete response: 0
- Partial response: 54%
- No change: 45%
- Progressive disease: 1%

They conclude that the leuprorelin acetate depot suppressed serum luteinising hormone, follicle stimulating hormone and testosterone concentrations. Objective response rates of the prostate, bone metastases, serum prostatic acid phosphatase and soft tissue metastases, and subjective dysuria and pain responses were comparable to those found with conventional hormone therapy. The leuprorelin acetate depot was well tolerated, with no significant differences in response to the two doses.

Efficacy in neo-adjuvant therapy

Zelefsky & Harrison (1997) sought to determine the impact of neo-adjuvant hormone therapy (NHT) prior to conformal radiotherapy on the reduction of volume of normal tissue structures exposed to high doses of radiation therapy and to evaluate the overall late toxicity and response to treatment among patients treated with this approach.

Among 214 patients treated with leuprorelin and flutamide for 3 months prior to three-dimensional conformal radiotherapy, 45 patients were prospectively evaluated with detailed dose-volume histogram analyses to determine the extent of improvement of the geometry of the target volume after NHT.

In the 45 patients evaluated, the median reductions of the rectal and bladder volumes receiving 95% of the prescription dose were 18% and 46% respectively, while 91% showed a reduction of small bowel volume in a range of 27% to 100% of the prehormonal values.

Among the entire group of 214 patients treated with NHT and 3D-CRT, no WHO grade 3 or 4 toxicity was observed with a median follow-up of 15 months. The 3-year actuarial grade 2 late gastrointestinal and genitourinary toxicity rates were 6% and 1% respectively.

The authors concluded that the unfavourable geometry associated with bulky prostatic disease can be improved with effective hormonal cytoreduction and that curative radiotherapy doses can be delivered after such hormonal therapy, to the prostate and seminal vesicles, while respecting the tolerance of surrounding normal tissues.

Overview of studies performed with LHRH agonists in general in non-metastatic disease

A Cochrane Review (*Kumar et al 2006*) concluded that:

- Hormone therapy combined with either prostatectomy or radiotherapy is associated with significant clinical benefits in patients with local or locally advanced prostate cancer.
- Significant local control may be achieved when given prior to prostatectomy or radiotherapy, which may improve the patient's quality of life.
- When given adjuvant to these primary therapies hormone therapy not only provides a method for local control but there is also evidence for a significant survival advantage.

A second review by *Gommersall et al (2002)* and a meta-analysis by *Boustead & Edwards (2007)* concur in concluding a valuable role for ADT exists in the treatment of non-metastatic prostate cancer.
In addition, *Persad (2002)* has reviewed the literature relating specifically to leuprorelin in Europe and has come to a similar conclusion.
Furthermore, the expert guidelines issued in 2007 by the European Association of Urology, The European Society of Clinical Oncology, the US National Comprehensive Cancer Network, the American Urological Association and NICE, quoted under 'Guidelines' above, are all based on thorough and recent reviews of the literature.

Conclusion
Based on general practice reflected in the applicable guidelines, studies performed in locally advanced prostate cancer with leuprorelin and meta-analyses of studies of LHRH agonists in general, the benefit of leuprorelin for this group of patients is considered established. Based on the study results, the risk profile is regarded the same as in treatment of metastatic prostate cancer. In the Board meeting of 29 October 2009, the Board expressed its approval of the extended indication. The type II variation was finalised with a positive outcome on 23 November 2009.

Literature references

Abbou CC, Lucas C, Leblanc V. Tolerance and clinical and biological responses during the first 6 months of treatment with 1-month sustained release LHRH agonists leuprorelin and triptorelin in patients with metastatic prostate cancer. Prog Urol 1997; 7(6): 984-95.

Akaza H, Aso Y, Koiso K, Fuse H, Isurugi K, Okada K, et al. Leuprorelin acetate depot: results of a multicentre Japanese trial. TAP-144-SR Study Group. J Int Med Res 1990;18 Suppl 1: 90-102.

Bischoff W. 3.75 and 7.5 mg leuprorelin acetate depot in the treatment of advanced prostatic cancer: preliminary report. German Leuprorelin Study Group. J Int Med Res 1990;18 Suppl 1: 103-13.

Bourdin S, Karam G, Clemain P, Bouchot O, Peuvrel P, Lacoste J, et al. Clinical experience with leuprorelin acetate before radiotherapy for prostatic cancer. J Int Med Res 1990;18 Suppl 1:74-8.

Boustead G, Edwards SJ. Systematic review of early vs deferred hormonal treatment of locally advanced prostate cancer: a meta-analysis of randomized controlled trials. BJU Int 2007; 99(6):1383-9.

D'Amico AV, Manola J, Loffredo M, Renshaw AA, DellaCroce A, Kantoff PW. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. JAMA 2004; 292(7):821-7.

Gommersall LM, Hayne D, Shergill IS, Arya M, Wallace DM. Luteinising hormone releasing hormone analogues in the treatment of prostate cancer. Expert Opin Pharmacother 2002; 3(12): 1685-92.

Kumar S, Shelley M, Harrison C, Coles B, Wilt TJ, Mason MD. Neo-adjuvant and adjuvant hormone therapy for localised and locally advanced prostate cancer.
Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No.: CD006019. DOI: 10.1002/14651858.CD006019.pub2.

Persad R. Leuprorelin acetate in prostate cancer: a European update. J Urol Urogynakol 2002; (3)16-25

Wechsel HW, Zerbib M, Pagano F, Coptcoat MJ. Randomized open labelled comparative study of the efficacy, safety and tolerability of leuprorelin acetate 1M and 3M depot in patients with advanced prostatic cancer. Eur Urol 1996; 30 Suppl 1: 7-14.

Zelefsky MJ, Harrison A. Neoadjuvant androgen ablation prior to radiotherapy for prostate cancer: reducing the potential morbidity of therapy. Urology 1997; 49 (3A Suppl): 38-45.