C B G
M E B

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Leuproreline Sandoz depot 3 maanden 5 mg, implant
Sandoz 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 30594

6 August 2012

Pharmacotherapeutic group:	gonadotropin releasing hormone analogues
ATC code:	L02AE02
Route of administration:	subcuteneous
Therapeutic indication:	metastasized prostate carcinoma, in which suppression of the testosterone production is desired
Prescription status:	prescription only
Date of authorisation in NL:	2 August 2006
Application type/legal basis:	Directive 2001/83/EC, Article 10(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 Leuproreline Sandoz depot 3 maanden 5 mg, implant from Sandoz B.V. The date of authorisation was on 2 August 2006 in the Netherlands.

The product is indicated for treatment of metastasized prostate carcinoma, in which suppression of testosterone production is desired.

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 so-called hybrid application claiming essential similarity with the innovator product Lucrin® Depot 11.25 mg, powder and solvent for suspension for injection containing 11.25 mg leuprorelin acetate (NL License RVG 21165), which has been registered in the Netherlands since 19 November 1997 by Abbott B.V. It concerns a hybrid application, as there is a difference in pharmaceutical form (implant vs. powder for suspension for injection).

The marketing authorisation is granted based on article 10(3) of Directive 2001/83/EC hybrid application, as bioequivalence cannot be demonstrated through bioavailability studies.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for hybrid products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. The MAH has submitted two dose-finding phase I studies 99-62-IMP-5 and 2001-01-IMP-7 (HEX1), and two pivotal clinical phase III studies 2001-33-IMP-8 (HEX2) and 2001-34-IMP-9 (HEX3). These two pivotal studies have also been evaluated by meta-analysis (HEX4).

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

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 active substance is freely soluble in water. The drug substance is isolated by a lyophilisation procedure and therefore obtained as an amorphous powder. Besides this, no crystalline or polymorphic forms are known. Due to its amorphous character the drug substance displays a highly heterogeneous particle size distribution.

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 specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 batches.

Stability of drug substance
The active substance is stable for 36 months 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
Leuproreline Sandoz depot 3 maanden 5 mg is a white to white slightly yellowish, biodegradable implant with uniform surface, containing 5 mg leuproreline.

The product is packed in a sterile transparent glass syringe in a sterile polyethylene terephthalate /aluminium/PE sachet.

The only excipients is polylactic acid.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Due to the very low oral bioavailability, leuprorelin has to be administered

parenterally. The only excipient used is a polymer matrix. Literature confirmed that the type of polymer is often used as biodegradable excipient
The product is terminally sterilized in its final container by gamma-irradiation. The MAH demonstrated that the irradiation dose has no negative impact on the quality of the product.
The aim of developing the implant has been sufficiently described as well as the description of release mechanism. Overall, the pharmaceutical development has been sufficiently elucidated.

Manufacturing process
The manufacturing process consists of three main steps:
- production of the powder batches,
- production of implants by extrusion,
- packaging and terminal sterilisation.

The manufacturing process has been described in a detailed manner and has been validated for a sufficient number of batches.

Control of excipients
In-house specifications were presented for polylactic acid. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification and includes tests for appearance, functionality of delivery system, uniformity of mas, identification, assay, content uniformity, related substances, water content, sterility, bacterial endotoxins and microbiological purity. Satisfactory validation data for the analytical methods have been provided.
Batch analytical data from 7 batches have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for 3 batches during storage at 25°C/60% RH (48 months), 30°C/65% RH (36 months) and 40°C/75% RH (12 months). All parameters tested within specifications. No photostability studies have been performed, but these are not necessary considering the packaging. Based on the data submitted, a shelf life was granted of 48 months. The labelled storage conditions are 'Do not store above 30 ºC'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non-clinical aspects

Pharmacodynamics
Leuproreline acetate is a synthetic nonapeptide analogue of the naturally occurring gonadotropin-releasing hormone (GnRH) and acts as a gonadorelin agonist. Its agonistic effect resulted from the substitution of the 6th amino acid in the native molecule with D-leucine.
The general pharmacological properties of leuprorelin have been characterized in generally accepted models *in vitro* and *in vivo*. Leuprorelin produced a drastic suppression of gonadotropin and sex hormone levels and induced changes in weight of genital organs in both males and females in various animal species. Serum LH, FSH and testosterone was strongly suppressed *in vivo*, after an initial flare-up of these hormones, disappearing almost completely within several days to weeks. Studies in animal models of prostatic cancer, endometriosis and uterine fibroma indicated therapeutic benefit.
The main mechanism of action is pituitary desensitisation. Leuprorelin acetate is a potent agonist analogue of gonadotropin releasing hormone (GnRH) , and initially induced release of gonadotropins (LH, FSH) from the anterior pituitary. With continued exposure, it causes desensitisation and/or downregulation. Gonadotropins control release of testosterone from the Leydig cells in males and estrogen from the ovaries in females. The suppression of gonadotropin hormones results in suppressed sex hormone levels.

Effects not related to the therapeutic activity of leuprorelin were few. In animal studies, leuprorelin was well tolerated.

Pharmacokinetics
The kinetics of leuprorelin and testosterone suppression in serum have been studied in beagle dogs. After an initial peak, leuprorelin concentration was maintained for up to 3 months. Testosterone concentration showed an initial flare reaction, followed by a fall to castrate levels for over 3 months. Leuproreline Sandoz kinetics is dose-proportional after s.c. administration, but differs from Lucrin pharmacokinetics. However, testosterone suppression was comparable with all leuprorelin formulations and Lucrin in one study (HEX1), and longer lasting in Leupro 3M formulations in another study (HEX2). The initial burst effect is dose-proportional between 5 and 10 mg Leupro 3M and lower than that of Lucrin. The poly-L,D-lactide appears to be appropriate carrier for the leuprorelin formulation. Only great differences in the relative molecular weight may affect the pharmacokinetic profiles and the biological activity in terms of testosterone suppression. Pharmacokinetic drug interactions were not reported in animals.

Toxicology
Acute toxicity of leuprorelin depot is low in rats and mice. In repeated-dose studies, effects observed were mainly pharmacodynamic effects. Additional effects were a decrease of growth and body weight in males, and an increase of these parameters in female animals, a decrease in kidney weight, and a decrease of bone mineral density. These effects were observed at doses sufficiently in excess of therapeutic doses to be used in humans.
Fertility was not impaired in male rats given s.c. leuprorelin doses up to 2.4 mg/kg/4 weeks during 12 weeks. Female fertility decreased at 200 µg/kg/day (decreased mating performance, decrease litter number). No evidence of teratogenicity was observed in mice and rats, when leuprorelin was administered s.c. during organogenesis at doses up to 80 µg/kg. However, in rats and rabbits foetal mortality was increased, and foetal weight decreased at clinically relevant doses. In rabbits, embryolethality was observed at doses ranging from 0.1 to 1 µg/kg/day, which is also clinically relevant.
In studies submitted by the MAH, it is indicated that the local tolerance of the leuprorelin formulation was good, both in dogs and rabbits. In literature studies in dogs, mild effects were observed. The excipient poly-L,D-lactide is also well tolerated. Impurities are detected at amounts, which cannot be expected to interfere with the benefit/risk ratio of the formulation.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of leuprorelin released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

II.3.1 Introduction
Leuprorelin is a well-known active substance with established efficacy and tolerability.

For this hybrid application, the MAH has submitted three studies and a meta-analysis. The following studies are reported:

HEX 1
Two dose- finding phase I studies
Study 1: Explorative study on efficacy and pharmacokinetics of leuprorelin after subcutaneous implantation of two different novel leuprorelin formulations in 12 healthy males. Study No. 99-62-IMP-5; PIM 2924. 2001. The pharmacokinetics of leuprorelin and pharmacodynamics of testosterone were studied following the administration of different batches and different doses (5 mg and 10 mg).
Study 2: Explorative parallel group study on efficacy and pharmacokinetics of leuprorelin after subcutaneous implantation of two different novel leuprorelin formulations in eight healthy males. Study No. 2001-01-IMP-7; SCO 5005. 2002.

HEX 2
Randomized, open label, multicentre, phase III study on pharmacokinetics, pharmacodynamics, efficacy and safety of Leuprorelin implant in 56 subjects with advanced Prostate cancer in comparison to Trenantone. Study No. 2001-33-IMP-8. 2003.

HEX 3
Open label, multicentre, phase III study on pharmacokinetics, pharmacodynamics, efficacy and safety of Leuprorelin implant in 30 patients with advanced prostatic cancer. Study No. 2001-34-IMP-9. 2003.

HEX 4 (Meta-analysis)
Meta-analysis of the clinical studies **HEX 2** and **HEX 3**.

The formulation at issue has been compared with Trenantone® (registered in Germany), a powder for suspension for injection, containing 11.25 mg leuprorelin acetate. In contrast with the microcapsules formulation of the originator with a drug content of 10.72 mg leuprorelin per dose, the studies are carried out with a biodegradable implant with a drug content of 5.25 mg leuprorelin acetate per dose.

Therapeutic indication
Carcinoma of the prostate is the most common neoplasm in men over 65 years and the second most common cause of cancer death in this patient population. The hormone dependency and the clinical response to androgen deprivation was recognised about 50 years ago. Treatment aims at lowering the levels of circulating androgens (i.e. testosterone) below the castration level, since most prostate cancers are testosterone dependent. Testosterone suppression is a valid surrogate parameter for the clinical efficacy of this kind of treatment for prostatic cancer.
Androgen deprivation or suppression can be achieved by bilateral orchiectomy, hormonal therapy with estrogens or antiandrogen compounds, and with GnRH agonists, such as leuprolide (leuprorelin) acetate, administered as depot formulations.

Leuprorelin acetate is a synthetic, potent analogue of GnRH naturally released from the hypothalamus. GnRH is a collective term that includes both FSH-releasing hormone (FSH-RH) and LH-releasing hormone (LH-RH). GnRH initially stimulates the release of gonadotropins including LH and FSH, which control the release of testosterone from testicular Leydig cells in men and estrogens from the ovaries in women. Continuous administration (i.e. chronic, non intermittent use) leads to hypohyseal desensibilisation, resulting in lowered testosterone in the male and lowered estrogen to postmenopausal values in the female.

Quality of clinical studies, compliance with GCP
The clinical studies were mainly conducted in Europe and all were performed in compliance with ICH GCP.

II.3.2 Clinical studies

HEX 1

Design
Study Participants
Subjects: 20 non-hypogonadal healthy elderly men, aged 45 to 70.

Treatments
Treatment a: a total of 10 subjects were treated with 5 mg leuprorelin (corresponds to 5.25 mg leuprorelin acetate).
Treatment b: 10 subjects with a single dose of 10 mg leuprorelin (corresponding to 2 x 5 mg implants supplied in the same syringe).

Objectives

Primary parameters were duration of testosterone suppression to values below the castration level (0.5 ng/ml) and leuprorelin pharmacokinetics. *Secondary parameters* were concentration-time course of LH, FSH and DHT.
FSH, testosterone and dihydrotestosterone (DHT) were evaluated as a surrogate for the efficacy.
The studies were regarded as completed in a subject, if the testosterone levels had returned to normal levels.

Efficacy
The data concerning testosterone after successful application of leuprorelin are presented below in Figure 1 and Table 1.

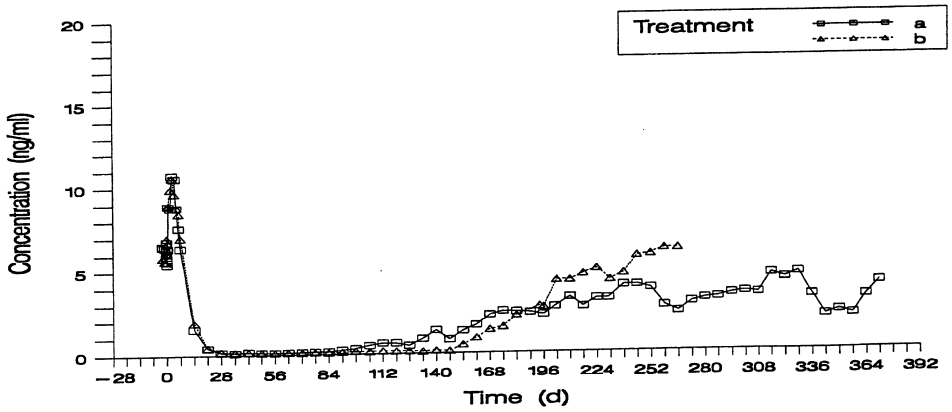

Figure 1 Mean testosterone serum concentrations following single dose administration of 5 mg leuprorelin (treatment a) to 10 healthy subjects and 10 mg leuprorelin (treatment b) to 10 healthy subjects.

	Treatment a					Treatment b				
	C_{max} ng/ml	t_{max} d	AUC0-21 ng/ml d	tfirst C<0.5 d	Tw(C< 0.5) d	C_{max} ng/ml	t_{max} d	AUC0-21 ng/ml d	tfirst C<0.5 d	Tw(C< 0.5) d
MEAN	11.23	3.08	95.55	25.20	154.61	11.15	2.99	102.08	23.80	154.70
STD	5.15	1.37	39.15	9.45	46.15	2.67	1.15	24.18	3.61	18.09
CV	45.85	44.3	40.98	37.50	29.85	23.93	38.6	23.69	15.19	11.69
MIN	4.68	0.99	36.86	14.00	61.03	7.43	1.00	51.38	21.00	123.26
MED	11.15	2.99	88.44	21.00	172.13	10.51	2.99	103.91	21.00	157.98
MAX	23.07	5.97	163.73	49.00	205.42	15.57	4.99	132.83	28.00	180.42
GeoM	10.27		88.16			10.86		98.94		
GeCV	47.07		45.77			24.52		28.44		

Table 1a

Model	Variable	PE %	LL90 %	UL90 %	ANOVA-CV %
y=f(TRT)	AUCo-21 log	89.1	67.1	118.3	37.9
	C_{max} log	94.6	71.6	125.0	37.1
	Tw(c<0.5) lin	-0.1 d	-27.3 d	27.1 d	22.7
		99.9	82.4	1 17.5	22.7
y=(SUBJ, TRT)	AUC0-21 log	100.3	63.5	158.4	19.4
	C_{max} log	89.2	76.7	103.7	6.3
	Tw(c<0.5) lin	-14.2	-70.0	41.5	14.5
		91.2	56.8	125.7	14.5

Table 1b

Table 1 Table 1 a and b: the pharmacokinetic parameters of **testosterone** after treatment a and treatment b (upper panel) and the 90% confidence intervals for the ratios or differences of treatment a versus treatment b (lower panel) in 10 healthy volunteers.
Abbreviations: AUC0-21 area under the curve from day 0 to day 21; AUC0-168 area under the curve from day 0 to day 168; tfirst c<0.5 first time with testosterone concentration <castration level 0.5 ng/ml; Tw(c<0.5) duration of testosterone suppression < castration level. STD standard deviation, GeoM geometric mean, PE point estimate, LL lower limit, UL upper limit, CV coefficient of variation.

It may be concluded that both doses of the new leuprorelin depot formulation equally suppressed the endogenous testosterone below the castrate level of 0.5 ng/ml and showed comparable concentration-time profiles of this parameter. Since testosterone is a valid surrogate parameter it is concluded that both dose levels of the new leuprorelin implant will be efficacious under therapeutic conditions. Therefore treatment a can be considered as a lower effective dose.
The pharmacodynamic response to the leuprorelin application does not differ between the two doses and this is true for the whole cascade of events effected by leuprorelin application. The action of leuprorelin is biphasic. The application of the implant causes an initial burst of LH and subsequently of testosterone and of DHT. Three to four weeks after application the hormone production is suppressed to a minimum. In all subjects the recovery from the testosterone suppression did not start before day 91 after application.
With respect to the primary variable duration of testosterone suppression under castration level, the lower leuprorelin dose had the same effect as the higher dose.

Safety
Adverse events were recorded by regular questionnaires or whenever they occurred they were spontaneously reported. Of the 67 adverse events observed during drug exposure period, 55 adverse events were classified as possibly related (possible, probable, certain) to the study drug: 26 adverse events during treatment a and 29 adverse events during treatment b. Twelve adverse events were categorized as unlikely related. Of the 12 adverse events observed during the periods without drug administration, 8 adverse events were classified as (at least) possibly related and 4 adverse events as unlikely related. In 11 events corrective treatment was necessary. Three serious adverse events occurred in 1 subject (relationship unlikely). Altogether 73 adverse events resolved completely but 2 adverse events were unchanged and 4 improved but were still present at study discontinuation. No relevant differences in the incidence or pattern of adverse events were observed between the treatments.
The most frequently reported adverse events were hot flushes and reduced libido (17 events), followed by sleep disturbance (6 events), respiratory tract disease (RTD) and common cold (4 events, respectively). The intensity of the adverse events was mild in 38 cases, moderate in 36 cases, 5 events had a severe intensity.
Hot flushes with sleep disturbance represented also the most relevant side-effects. In altogether 6 subjects concomitant medication was observed, in all cases for treatment of adverse events. In 5 subjects testosterone substitution was performed in order to relieve adverse effects resulting from testosterone suppression. This substitution was administered as 1 or 2 testosterone patches daily containing 2.5 mg testosterone for a certain period during the study. The subjects were advised to apply a patch-free interval of at least 24 h prior to the next scheduled visit in order to not confound testosterone levels. In addition, the administration of concomitant medication was observed in 3 subjects for adverse events. No implication of the study results was expected from the concomitant medications. No further co-medication was observed.
Another effect possibly related to testosterone suppression was a tendency for body weight increase in most subjects. The frequency indicated a relevant metabolic effect.
There were no deaths. Three serious adverse events occurred (all in one subject) with unlikely relationship to the study drug.

Altogether 73 adverse events resolved completely, but 2 adverse events were unchanged, 4 improved but were still present at the end of the study: weight increase, increase in blood pressure and heart rate, abnormal ECG, and chronic lung disease. No relevant differences in incidence or pattern of adverse events were observed between the treatments.

	Treatment a	Treatment b
Number of adverse events	**26**	**29**
Subjects reporting AE	**10**	**10**
hot flushes	7/7	9/9
reduced sexual impulse	7/7	9/9
sleep disturbance	5/5	1/1
headache	1/1	1/1
pain on application site	1/1	1/1
sweating	1/1	1/ 1
urgency	1/1	1/1
weight increase	1/1	1/1
depressive mood	./.	1/1
hepatic enzyme elevation (GGT, GPT, AP)	./.	1/1
hyperuria	1/1	./.
increased appetite	./.	1/1
increased lacrimal flow	./.	1/1
nocturia	./.	1/1
vertigo	1/1	./.

Table 2. Drug-related adverse events in healthy elderly volunteers

HEX 4: Meta-analysis of clinical studies HEX 2 and HEX 3.

Design

Methods

Definitions:

- safety population: including all subjects who received study medication
- efficacy population: excluding any subjects who had received previous or concurrent medication for prostate cancer, with the exception of medication for distal bone metastases
- valid case population: excluding subjects without valid termination of testosterone data

Analysis of efficacy was based on the valid case and the efficacy population.

Study population

The study population subject to meta-analysis is presented in the Table 3.

Population	Leupro 3M (N)	Trenantone® (N)	Total (N)
Screened	126		126
Randomized	66	28	94
Safety population (received study medication)	64	28	92
Excluded due to prohibited co-medication	*1*	-	*1*
Efficacy population	63	28	91
Lacking valid data at weeks 12/16	*5*	*2*	*4*
Valid case population	58	26	84

Table 3 The study populations of the Clinical Studies 2001-33-IMP-8 (**HEX 2**) and 2001-34-IMP-9 (**HEX 3**), subject to meta-analysis in **HEX 4**.

Diagnosis and criteria for inclusion in **HEX2** and **HEX3** were: histologically confirmed advanced adenocarcinoma of the prostate, stage $T_{3-4}N_0M_0T_{1-4}N_1M_0$ or $T_{1-4}N_{0-1}M_1$, newly diagnosed or recurrent; age >18 and < 85 years; morning testosterone level > 2.3 - 3 ng/ml at screening.

Most of the subjects in each treatment group were classified as TNM grade 3a-0-0. The most common histopathological grades were G2 and G3 in both treatment groups:

Histopathological stage	Number of subjects (%)	
	Leupro-3M (N=63)	Trenantone® (N=28)
G1	12 (19%)	6 (21%)
G2	22 (35%)	14 (50%)
G3	18 (29%)	7 (25%)
G3-4	5 (8%)	1 (4%)
G4	5 (8%)	0 (-)
GX	1 (2%)	0 (-)

Table 4 The histopathological stage at screening (efficacy population)

Treatments
Test (treatment **a**) Leupro 3M (5 mg leuprorelin corresponding to 5.25 leuprorelin acetate)
Reference (treatment **b**) Trenantone (10.72 mg leuprorelin corresponding to 11.25 mg leuprorelin acetate); the reference medicinal product marketed in the Netherlands: Lucrin Depot 11.5 mg; leuprorelin acetate 11.25 mg, powder for suspension for injection.

Objectives
Primary efficacy evaluation:
- successful testosterone suppression
- testosterone levels <0.5 ng/ml until week 12

Secondary efficacy endpoints:
- escapes of testosterone level
- testosterone levels at weeks 4,8,12 and 16
- time to onset of castration level
- duration of suppression
- change in prostate status (digital rectal examination)
- change in PSA and PAP
- subjective response by WHO performance scale
- subjective clinical symptoms due to prostate cancer (dysuria, nycturia, bone pain)
- overall efficacy as judged by the investigator and subject
- serum profiles of LH, FSH, DHT, E_2 and SBHG
- pharmacokinetics of leuprorelin and testosterone

Pharmacokinetics in patient population
Leuprorelin pharmacokinetic data in patients with advanced prostatic cancer were obtained from the pivotal studies 2001-33-IMP-8 (HEX2) and 2001-34-IMP (HEX3). In study 2001-34-IMP (HEX3) pharmacokinetics were obtained following a single dose administration of 5 mg leuprolelin, whereas in study 2001-33-IMP (HEX2) a single dose of 5 mg leuprorelin was compared with a 10.72 mg leuprorelin dose of the Trenantone® innovator.

	Study 2001-34 IMP-9(HEX3)	**Study 2001-33 IMP-8(HEX2)**

	5 mg leuprorelin test	5 mg leuprorelin test	10.72 mg leuprorelin reference
N	29	27	26
AUC_{0-28d} (pg/ml d)	22480 ± 7914	18390 ± 6412	11220 ± 5632
AUC_{0-84d} (pg/ml d)	34920 ± 12470	34090 ± 15280	17070 ± 7759
AUC_{0-140d} (pg/ml d)	41190 ± 12980	41650 ± 17600	21420 ± 10220
AUC_{0-last} (pg/ml d)	41530 ± 12900	41830 ± 17640	22030 ± 10740
C_{max} (pg/ml)	6148 ± 2206	5901 ± 2054	12950 ± 6130
t_{max} (h)	2.0 (0.25-6.0)	2.0 (0.93-4.1)	3.0 (1.0-6.0)

Table 5 Leuprorelin pharmacokinetic parameters obtained from studies 2001-33-IMP-8 (HEX2) and 2001-34-IMP-9 (HEX3) as mean ± SD (t_{max} as median (range).

The relative bioavailability of the 5 mg test leuprorelin formulation and the 10.72 mg leuprorelin Trenantone® reference formulation was investigated in study 2001-33-IMP-8 (HEX2). For this purpose, 90% confidence intervals were calculated following log-transformation of the AUC and C_{max} values. Furthermore, t_{max} were compared non-parametric methods. The results are summarised in Table PK3.

Parameter	Ratio test/ref (90% CI)	ANOVA-CV %
AUC_{0-28d} (%)	1.73 (1.45-2.07)	40.5
AUC_{0-84d} (%)	2.20 (1.67-2.45)	43.3
AUC_{0-140d} (%)	2.01 (1.64-2.46)	46.5
AUC_{0-last} (%)	1.97 (1.60-2.43)	47.4
C_{max} (%)	0.48 (0.40-0.56)	47.5
t_{max} (h)	-1.0 (-0.195- -0.08)	-

Table 6 Ratio test/reference leuprorelin (90% CI) following single dose administration of 5 mg leuprorelin test and 10.72 mg leuprorelin Trenantone® reference formulation in patients with advanced prostate cancer **(**Study 2001-33 IMP(HEX2)).

The bioavailability of the 5 mg leuprorelin depot is higher than that of the 10.72 mg leuprorelin Trenantone® reference formulation. The test/reference $AUC_{0-84\ days}$ ratio (90% CI) was 2.20 (1.67-2.45).

Efficacy

Primary efficacy endpoints

The primary efficacy evaluation is presented in the next table:

Treatment	N	Successful N (%)	Unsuccessful N (%)	95% CI lower limit
Week 8 Valid case population				
Leupro 3M	58	57 (98%)	1 (2%)	92.1%
Trenantone®	26	21 (81%)	5 (19%)	63.7%
Efficacy population				
Leupro 3M	63	60 (95%)	3 (5%)	88.2%
Trenantone®	28	22 (79%)	6 (21%)	62.0%
Week 12 Valid case population				
Leupro 3M	58	57 (98%)	1 (2%)	92%
Trenantone®	26	21 (81 %)	5 (19%)	63.7%
Efficacy population				
Leupro 3M	63	57 (90%)	6 (10%)	82.1%
Trenantone®	28	21 (75%)	7 (25%)	58.1%
Week 16 Valid case population				

Leupro 3M	58	55 (95%)	3 (5%)	87.2%
Trenantone®	26	19 (73%)	7 (27%)	55.3%
Efficacy population				
Leupro 3M	63	55 (87%)	8 (13%)	78.3%
Trenantone®	28	19 (68%)	9 (32%)	50.6%

Table 7 Proportion of subjects with successful testosterone suppression

Secondary efficacy endpoints
All secondary efficacy endpoints were evaluated for the efficacy population.

There was no *testosterone escape* in the Leupro 3M group and one under Trenantone®

Testosterone levels at weeks 4, 8, 12 and 16
There were no relevant differences in testosterone levels between groups at weeks 4,8, 12 and 16 and median testosterone concentrations remained stable throughout the study. The data are given in the next Table.

	Leupro 3M				**Trenantone®**			
	Week 4	Week 8	Week 12	Week 16	Week 4	Week 8	Week 12	Week 16
N	60	61	57	56	26	24	22	23
Median	0.30	0.30	0.30	0.30	0.40	0.29	0.20	0.30
Range	0.10-0.70	0.10-0.80	0.10-0.50	0.10-3.50	0.10-2.40	0.10-1.00	0.10-0.50	0.10-0.70

Table 8 Testosterone levels at weeks 4, 8, 12, 16

Time to onset of castration level (≤ 0.5 ng/ml)
The median for the time to onset of castration level was approximately 3 weeks for both groups (3.1 weeks for Leupro 3M and 3.2 weeks for Trenantone®). However, the time to onset of castration level varied less in the Leupro 3M group (range of 2 –6.1 weeks) than under Trenantone® (range of 2- 12 weeks). The data are given in Table 9.

	Leupro 3M	**Trenantone®**
N	63	28
Median	3.1	3.2
Range	2.0 - 6.1	2.0 -12.0

Table 9 Time to onset of castration level in weeks (Kaplan-Meier based statistics)

Duration of testosterone suppression
The median duration of testosterone suppression, defined as the last testosterone values < 0.5 ng/ml, was comparable for both groups, namely 19 weeks.

	Leupro 3M	**Trenantone®**
N*	61	25
Median	19.0	19.0
Range	7.0 - 32.1	4.3 - 26.0

Table 10 Duration of testosterone suppression (Kaplan-Meier based statistics); *subjects without suppression were not included.

Change in prostate status (DRE):
Prostate status of each subject, based on the rule of the DREs, as compared from study start to visits 19 and 31 (weeks 12 and 24) and to the final visit. At these visits, a similar proportion of subjects in both groups returned to normal while the proportion of subjects with >50% improvement was 32-35% higher in the Leupro 3M group as compared to Trenantone®. One subject under Leupro 3M presented with a 25%

worsened status at the final visit, 18 weeks after study begin while the interim assessment at week 12 had shown a status “similar to baseline”.

Treatment	Visit/Week	N (missing)	Number of subjects (%)			
			Returned to normal	>50% improvement	Similar to baseline	>25% worsened
Leupro 3M	19/12	57 (6)	2 (4%)	39 (68%)	16 (28%)	0 (-)
	Final	57 (6)	4 (7%)	36 (63%)	16 (28%)	1 (1.8%)
Trenantone®	19/12	22 (9)	2 (9%)	8 (36%)	12 (55%)	0 (-)
	Final	25 (6)	2 (8%)	7 (28%)	16 (64%)	0 (-)

Table 11 Change in prostate status (DRE) compared to screening (efficacy population)

Change in serum PSA and PAP

Median concentrations of serum PAP declined after baseline in both groups. By week 12 the median values of serum PAP were 1.1 ng/ml in the Leupro 3M group (2.5 ng/ml at baselin) and also 1.1 ng/ml in the Trenantone® group (2.85 ng/ml at baseline). The development of the median concentrations of serum PSA was comparable in both treatment groups. The percentages of subjects with normal PSA values (PSA ≤ 4 ng/ml) at each visit were similar for both groups, starting at about 13% at visit 1 for the Leupro 3M subjects and 18% for the Trenantone® subjects and steadily increasing after visit 8 up to values of 79% for Leupro 3M subjects and 78% for the Trenantone® subjects by week 16. Values thereafter were based on decreasing numbers of subjects and cannot really be compared. The decrease in PSA values from baseline until weeks 12 and 16 was also similar in both groups (Leupro 3M- 25.20 ng/ml and –23.80 ng/ml; Trenantone® -18.05 ng/ml and –21.90 ng/ml).

		Leupro 3M	Trenantone®
Baseline	N (missing)	49 (14)	22 (6)
Until week 12	Median	-25.20	-18.05
Baseline	N (missing)	55 (8)	23 (5)
Until week 16	Median	-23.80	-21.90

Table 12 Serum PSA (in ng/ml)

Subjective response - WHO performance scale

WHO performance status, indicating the general health and mobility, did not decline in any subject from baseline to final visit. The vast majority of Leupro 3M subjects remained at their baseline scores (91%) throughout the studies while 9% had improved. Similarly, 92% under Trenantone® had an unchanged WHO performance status while 8% improved.

Subjective clinical symptoms related to prostate cancer

Most subjects in both treatment groups had either improvements or no change in their subjective clinical symptoms of dysuria, nycturia or bone pain at their final visit.

Dysuria: of 57 evaluable Leupro 3M subjects; 30 (53%) improved, 24 (42%) remained the same and 3 (5%) had more intense symptoms while of the 25 Trenantone® subjects; 17 (68%) improved and 8 (32%) remained unaltered.

Nycturia: of the 57 evaluable Leupro 3M subjects; 25 (44%) improved, 29 (51%) remained unaltered and 3 (5%) experienced more intense symptoms while of the 25 Trenantone® subjects; 10 (40%) improved and 15 (60%) were unaltered.

Bone pain: of 57 evaluable Leupro 3M subjects; 4 (7%) improved and 53 (93%) were without change while of the 25 Trenantone® subjects; 5 (20%) improved and 20 (80%)
did not change.

Overall efficacy by investigator and subject

More than 90% of investigators and subjects rated the overall efficacy of Leupro 3M as good or very good at the final visit and more than 85% of investigators and subjects rated the overall efficacy of Trenantone® as good or very good at the final visit. Only minor differences between the ratings were noted.

Endocrine response
The profiles of mean serum LH, FSH, DHT, E_2 and SHBG were similar for the 2 treatment groups.

Testosterone kinetics/pharmacodynamics
The extent of the initial testosterone flush was similar after both products. The test product showed a slightly earlier onset and a longer duration of the testosterone suppression below a castration level. The mean concentration-time profile is depicted in the next Figure, Figure 2.

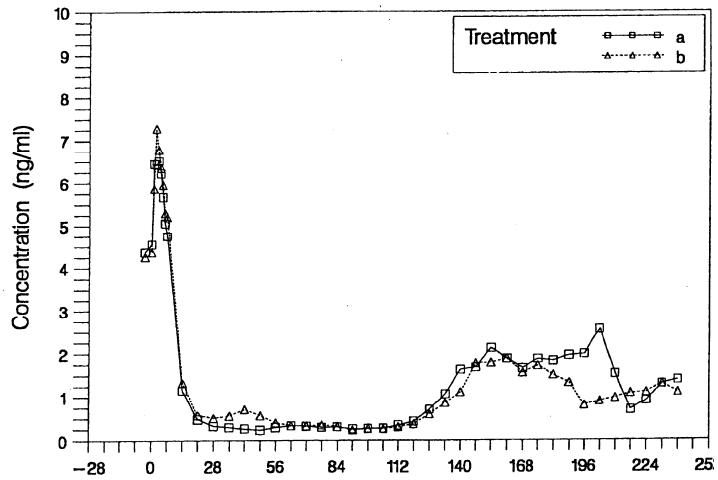

Figure 2 The time course of testosterone mean serum concentration following leuprorelin administration. Treatment a Leupro 3M, treatment b Trenantone®.

The population mean curves do not show major differences with respect to the time and height of the peak concentration and subsequent testosterone suppression. Three days after application of treatment a testosterone mean concentration attained a maximum of 6.52 ng/ml. After treatment b a maximum of 7.28 ng/ml was observed 2 days after application. Three weeks after application of both treatments the testosterone concentrations had dropped below the castration level of 0.5 ng/ml in the majority of patients. After treatment a this was observed in all patients 6 weeks after application by the latest whereas after treatment b 2 patients were non-responders completely lacking testosterone suppression below the castration level. The majority of patients remained below the castration level until day 133 after both treatments. Six months after application 27/58 subjects (treatment a) and 11/26 subjects (treatment b) still participated in the study. The patients discontinued the study when their testosterone concentrations exceeded 1 ng/ml on two subsequent visits.
The treatments were similar with respect to the acute testosterone response in terms of AUCO-21 (geometric means a 64.76 ng/ml d, b 68.86 ng/ml d), C_{max} (a 7.22 ng/ml, b 7.60 ng/ml) and t_{max} (medians 2.51 d and 2.05 d). This was also the case with the variables reflecting the subsequent testosterone suppression. The onset of the castration level (tfirst≤0.5) had median values of 22.09 d and 21.10 d, respectively. With respect to the mean duration of testosterone suppression (Twc≤0.5) a difference was detected between the treatments (arithmic means a 115.92 d, b 94.46 d). A difference also existed with respect to standard deviation (SD) being 26.45 d after treatment a as compared to 44.25 d after treatment b. The time points of the re-increase of testosterone beyond the castration levels (medians a and b: 133.05 d) did not differ between treatments. Data are given in the next table.

Treatment	Statistics	AUC0-21 ng/ml d	Cmax0-21 ng/ml	t_{max} 0-21 d	tfirstCt≤0.5ng/ml (d)	TwCt≤0.5 ng/ml (d)	tlastCt≤0.5 ng/ml (d)
a	N	58	58	58	58	58	58
	Mean	68.21	7.56	2.52	24.73	115.92	136.10
	SD	22.09	2.35	1.46	4.66	26.45	25.82

	CV	32.4	31.1	58.2	18.8	22.8	19.0-
	Min	23.34	2.60	0.00	14.02	27.01	49.01
	Med	62.75	7.20	2.51	22.09	115.63	133.05
	Max	132.40	15.00	7.00	35.05	196.00	224.98
	GeoM	64.76	7.22				
	G CV	34.0	32.1				
b	N	26	26	26	24	26	24
	Mean	71.98	7.77	2.54	29.66	94.46	130.50
	SD	21.10	1,64	1.15	15.67	44.25	29.01
	CV	29.3	21.1	45.3	52.8	46.8	22.2
	Min	35.05	4.00	0.97	14.00	0.00	30.05
	Med	69.16	7.75	2.05	21.10	110.84	133.05
	Max	118.95	11.43	5.04	84.05	163.75	182.06
	GeoM	68.86	7.60				
	G CV	32.0	22.6				

Table 13. The testosterone response to Leuprorelin. Treatment a: Leupro 3M, treatment b: Trenantone®.

Concentration-response relationship
The dose in test treatment was 5 mg leuprorelin, i.e. less than one half of the dose in treatment b (10.72 mg leuprorelin). In spite of the lower dose AUC was higher after treatment a than after treatment b. This relationship supports the higher bioavailability of leuprorelin from test formulation a as compared to b. The duration of testosterone suppression was slightly longer after treatment a which correlates with the higher extent of leuprorelin exposure after treatment a.

Point estimates and 90% Cis for the treatment ratios or differences are reported in Table 14:

Parameter		**Treatment**	**PE**	**LL90**	**UL90**	**Unit**	**ANOVA-CV %**
AUC0-21	log	a/b	94.0	82.8	106.9	%	33.4
Cmax	log	a/b .	95.0	84.8	106.4	%	29.5
Tmax[1]	lin	a-b	-0.025	-0.949	-0.121	D	
tfirst (CT≤0.5)[1]	lin	a-b	-0.02	-2.99	0.95	D	
TW (CT≤0.5)[2]	lin	a-b	11.8	0.37	27.3	D	34.8
tlast (CT≤0.5)[1]	lin	a-b	0.93	-6.98	13.9	D	

Table 14 Testosterone - 90% Confidence Intervals. REM: 1) non-parametric CI according to Mann/Whitney/Wilcoxon discrete distribution; 2) non-parametric CI according to Mann/Whitney/Wilcoxon significant p<0.01 deviation of the ANOVA residuals from normal distribution.

The point estimates suggest comparable acute testosterone responses to leuprorelin between the treatments. The AUC-21 ratio 94.0% (82.8%- 106.9%) and the C_{max} ratio (95.0%, 84.8%-106.4%) indicate a similar extent of the initial testosterone flush.
The most important parameter for the evaluation of the efficacy of leuprorelin is the onset (tfirstcT≤0.5) and the duration of the testosterone suppression (TWtc≤0.5). Also with respect to this parameter both leuprorelin formulations were similarly effective. The onset of suppression did not differ between the treatments, the difference of medians being –0.02 d (-2.99 d – 0.95 d). The duration of testosterone suppression was longer after the test preparation. The point estimate for the difference of the expected medians and the 90% CI were 11.8 d (0.37 d- 27.3 d).

Safety
The incidence of adverse events was comparable in both treatment groups. Comparable proportions of subjects in both groups experienced adverse events during the treatment phase (treatment-related adverse events, 32/64, 50% of the Leupro 3M subjects with 84 adverse events; 10/28, 36% of the Trenantone® subjects with 22 adverse events). One subject in the Leupro 3M group reported an AE (cystitis) during the run-in period.

Treatment-related adverse advents The numbers of treatment-related adverse events reported per subject are shown in the table below:

Treatment	N	No. of subjects (%) with respective number of adverse events						
		0	1	2	3	4	5	10
Leupro 3M	64	32	14	7	3	3	3	3
Trenantone®	28	18	2	4	4	0	4	0

Table 15 Number of treatment-related adverse events reported for each subject

There were no medically relevant differences for the most common body systems with adverse events or for the individual symptoms between the 2 treatment groups. One subject (1.6%) in the Leupro 3M group and 2 subjects (7%) in the Trenantone® group reported mild injection site reactions within 2 to 10 days after application.

Deaths
One subject died during the screening phase of study 2001-33-IMP-8) from a myocardial infarction. During the study, 4 subjects had adverse events resulting in death: 1 subject (Leupro 3M) had an aneurysm, 1 subject (Leupro 3M) due to the progression of his underlying disease, 1 subject (Trenantone®) had pneumonia, and 1 subject (Trenantone®) had bone metastases. All these serious adverse events were considered to be either unlikely related or unrelated to the study drug.

Serious adverse events
Four subjects had serious adverse events during the studies and all were serious because they resulted in death. There were no other serious adverse events.

Withdrawals due to adverse events
Four subjects withdrew due to adverse events resulting in death. No other subjects withdrew due to adverse events. (see Assessors comment below)

Adverse events by severity and relationship to study medication
Most of the treatment-related adverse events were either mild or moderate in severity. Three subjects in the Leupro 3M group had severe adverse events (urinary retention; aneurysm; progression of underlying disease), all of which were considered to be unlikely to be related to study drug. Four subjects in the Trenantone® group had severe adverse events (dysuria and nocturia; urinary retention; bone pain, bone metastases and pneumonia; bone metastases). Dysuria and nocturia and the bone metastases of in one subject were considered probably or possibly related to the study drug.
Twenty six subjects reported 41 treatment-related adverse events that were at least possibly related to the study drug (21 (33%) Leupro 3M subjects with 32 adverse events; 5 (18%) Trenantone® subjects with 9 adverse events). None of these were serious adverse events. These events were:
Leupro 3M subjects: hot flushes (16 subjects), generalised weakness (2 subjects), erection decreased (2 subjects), libido decreased (2 subjects), sleep disturbed (2 subjects), appetite lost (1 subject), dysuria (1 subject), SGPT increased (1 subject), injection site reaction (1 subject), perineal pain (1 subject), muscle pain (1 subject), abdominal pain upper (1 subject), dizziness (1 subject).
Trenantone® subjects: dysuria (2 subjects), nocturia (2 subjects), injection site reaction (2 x same subject), hot flushes (1 subject), bone metastases (1 subject), injection site pain (1one subject).

The incidence rate of hot flushes was higher in the Leupro 3M group (25%) than in the Trenantone® group (4%), but it was still less frequent than the published incidence rates of 48% to 59%.

Conclusions
The meta-analysis compared the pharmacokinetic profiles of leuprorelin under the test and the reference formulation and evaluated their activity in terms of testosterone suppression.

1) There were major differences between treatments with respect to leuprorelin AUC. The ratios of the pharmacokinetic parameters indicate average bioavailability of leuprorelin of the test preparation vs. the reference. The AUC_{0-84} ratio (CI 1.67-2.45) indicates that the bioavailability from the test preparation was twice as high when compared to the reference. Taking into account the dose of leuprorelin in the test preparation which amounts to only one half of that in the reference, bioavailability of leuprorelin from the test formulation is even 4 times higher than from the reference. For the rate characteristic C_{max} the relation between treatments was reversed. After the test formulation C_{max} of leuprorelin (test) amounted to 48.3%, 42.1 %-55.4%, as compared to the reference.

2) In contrast to leuprorelin disposition the serum profiles of testosterone were comparable under both formulations.

3) From a clinical point this is the reason why primary and secondary surrogate endpoints indicate comparable therapeutic impact under both regimens. The primary endpoints proportion of patients with successful testosterone suppression and with a testosterone level ≤0.5 ng/ml at week 12 demonstrated the efficacy of Leupro 3M vs Trenantone® in advanced prostatic cancer as all but one subject (57/58, 98%) achieved testosterone suppression within 8 weeks and suppression was maintained by all remaining subjects until week 12 and 16. Three and four months after application, 98% and 95% of the Leupro 3M subjects and only 81% and 73% of the Trenantone® subjects were still suppressed. Analyses of secondary therapeutic efficacy endpoints showed comparable results in both groups.

4) The analysis of the effects of doses in the range from approximately 5 - 10 mg leuprorelin in the clinical studies indicates that a maximal response is obtained with these doses. Therefore, on most of the parameters studied a ceiling effect is observed which lacks dose dependency.

Risk management plan
The safety profile of leuprorelin can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. 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 that accepted for the reference product Lucrin.

Readability test
The package leaflet has not been evaluated via a user consultation study test, as this was not required at the time of dossier submission.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Leuproreline Sandoz depot 3 maanden 5 mg, implant has a proven chemical-pharmaceutical quality and is a legitimate hybrid form of Lucrin Depot 11.25 mg, powder and solvent for suspension for injection. Lucrin Depot is a well-known medicinal product with an established favourable efficacy and safety profile.

In contrast with the microcapsules formulation of the originator containing 10.72 mg, the product is a biodegradable implant containing 5 mg leuprorelin. The MAH demonstrated efficacy and safety of the different pharmaceutical form by means of three studies and one meta-analysis, comparing the product to the innovator. Efficacy level was measured by the suppression of testosterone level. No clinically relevant difference with respect to efficacy or safety was observed between treatments.

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 no clinically relevant difference with respect to efficacy or safety has been demonstrated compared with the reference product, and has therefore granted a marketing authorisation. Leuproreline Sandoz depot 3 maanden 5 mg, implant was authorised in the Netherlands on 2 August 2006.

There were no post-approval commitments made during the procedure.

List of abbreviations

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
DRE	Digital Rectal Examination
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
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
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	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached