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.

<table>
<thead>
<tr>
<th>Registration number in the Netherlands: RVG 33195</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 June 2012</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacotherapeutic group:</th>
<th>gonadotropin releasing hormone analogues</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC code:</td>
<td>L02AE02</td>
</tr>
<tr>
<td>Route of administration:</td>
<td>subcutaneous</td>
</tr>
<tr>
<td>Therapeutic indication:</td>
<td>metastasized prostate carcinoma, in which suppression of the testosterone production is desired</td>
</tr>
<tr>
<td>Prescription status:</td>
<td>prescription only</td>
</tr>
<tr>
<td>Date of authorisation in NL:</td>
<td>9 January 2009</td>
</tr>
<tr>
<td>Application type/legal basis:</td>
<td>Directive 2001/83/EC, Article 10(3)</td>
</tr>
</tbody>
</table>

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.
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 1 maand 3.6 mg, implant from Sandoz B.V. The date of authorisation was on 9 January 2009 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 leuprorelin acetate 3.75 mg, powder for suspension for injection (NL License RVG 14351) which has been registered in the Netherlands since 21 June 1991 by Abbott B.V. It is on the market in other member states with different speciality names (Enantone®). It concerns a hybrid application, as there is a difference in pharmaceutical form (implant vs. powder for suspension for injection). The MAH has already obtained a marketing authorisation for a similar product with the same therapeutic indication, Leuproreline Sandoz depot 5 mg, implant (NL RVG 30594), registered since 2 August 2006. The 5 mg implant is administered as one shot every three months.

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 generic 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. To this end the MAH has submitted three studies and one meta-analysis: one study in healthy elderly men (HEX 1, s.c. implantation of the one-month leuprorelin implant against Enantone®; completed 19), two studies in prostatic carcinoma (HEX 2, implant against the German product Enantone® and HEX 3, implant; completed 75) and one meta-analysis (HEX 4). Both treatments are safe and well tolerated; there is no relevant difference in safety profile. This hybrid product can be used instead of its reference product.

No new pre-clinical studies were conducted, which is acceptable for this abridged application.

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, with additional requirements for residual trifluoroacetate and sterility (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 full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for 2 full-scale batches and 1 pilot-scale batch stored at 25°C/60% RH (24 months) and 40°C/75% RH (24 months). The batches were adequately stored. The granted re-test period is 24 months when stored below 30°C.

* 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 1 maand 3.6 mg is a white to white slightly yellowish, biodegradable implant with uniform surface, containing 3.6 mg leuprorelin (free base).

The product is packed in a sterile syringe which is sealed together with a desiccant in an aluminium sachet.

The only excipient is poly(lactic-co-glycolic acid) 50:50.

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, leuproreline has to be administered...
parenterally. The only excipient used is a polymer matrix. The choice of the matrix material was based on the type of matrix material that was used in the reference product. Furthermore, literature confirmed that the type of polymer, poly(lactic-glycolic) acid, is often used as biodegradable excipient. It has been studied what the influence of gamma irradiation is on the mean molecular weight of the polymer.

Both in vivo and in vitro experiments have been performed during the development phase. The implants are sterilised in the final container. Instead of thermal sterilisation, the MAH uses ionisation irradiation. The MAH demonstrated that the irradiation dose has no negative impact on the quality of the product.

In vitro studies focussing on the dissolution profiles using different types of polymer, have been performed as well as a possible in vitro/in vivo correlation. The manufacturing process development has been described in detail and can be considered adequate.

Overall, the pharmaceutical development has been sufficiently elucidated.

Manufacturing process
The manufacturing process consists of three main steps:
- production of the powder batches: mixture of active substance and excipient,
- production of implants by extrusion, cutting and weight sorting,
- packaging and terminal sterilisation.

The extrusion process is regarded a non-standard technique. However, as the capacity of the extruder is the limiting factor, the maximum filling capacity is considered to be production scale for this part of the production process. Adequate validation data for the three main steps have been provided for 3 full-scale batches.

Control of excipients
An in-house specification for the excipient has been laid down. This specification is acceptable.

Quality control of drug product
The product specification includes tests for appearance, functionality of delivery system, uniformity of mass, identification, assay, content uniformity, related substance, water content, dissolution and sterility. The requirements are identical at release and shelf-life, except for assay and two specified impurities. From stability results this is deemed feasible. The analytical methods have been adequately described and validated.

Batch analytical data from the proposed production site have been provided on 3 full-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided 3 full-scale batches stored at 25°C/60% RH (36 months), 30°/65% RH (36 months) and 40°/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in prefilled polycarbonate syringes packed with desiccant into PE-terephthalate/Al/PE sealable bags. Only minor degradation occurs. All parameters remain well within the predetermined parameters. The proposed shelf-life of 36 months and storage condition store below 30°C could therefore be granted.

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

This active substance has been available on the Dutch market for since 1991. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

Environmental risk assessment
The product is intended as a substitute for other comparable 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
II.3 Clinical aspects

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

In contrast with the microcapsules formulation of the originator containing 3.6 mg, the new product is a biodegradable implant containing 3.6 mg leuprorelin.

For this hybrid application, in support of the different pharmaceutical form, the MAH has submitted:
1) Study 2002-02-IMP-2, (HEX 1) an explorative study on pharmacokinetics, efficacy in terms of testosterone suppression and safety after subcutaneous implantation of the one-month leuprorelin implant (3.5 mg) against Enantone® (3.57 mg depot) in elderly healthy males;
2) Study 2002-18-IMP-3, (HEX 2) a randomized, open label, multicenter, phase III study of the one-month leuprorelin implant in patients with advanced prostatic cancer in comparison to Enantone®;
4) Meta-analysis of the studies 2) and 3) (HEX 4), concerning the efficacy of Leuproreline 1 month as compared with that of Enantone in the palliative treatment of advanced prostatic cancer.

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 hypophyseal desensibilisation, resulting in lowered testosterone in the male and lowered estrogen to postmenopausal values in the female.

GCP compliance
The MEB has been assured that clinical studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC). The studies were conducted in Europe.

II.3.2 Clinical studies

HEX 1: Study 2002-02-IMP-2

Design
This was an explorative study on efficacy in terms of testosterone suppression, pharmacokinetics of leuprorelin and safety after subcutaneous implantation of the novel one-month leuprorelin implant (3.5 mg) against Enantone® (3.57 mg depot suspension subcutaneous) in elderly healthy males. Two single doses were administered 4 weeks apart.
In part 1 of the study 6 subjects were treated with treatment A (2 single doses of implant, 4 weeks apart) and 6 subjects were treated with treatment B (2 single doses of Enantone®, 4 weeks apart). In part 2 of the study 9 subjects were treated with treatment A. In case a subject suffered seriously or subjectively too much from the testosterone suppression, testosterone substitution was offered (Androderm® patches in usual therapeutic doses). Testosterone supplementation was applied in two subjects only during the recovery period. The suppression thus did not have an impact on the testosterone dynamics. Twenty-one subjects were included: 15 for Leuprolelin implant and 6 for Enantone®. There were 2 drop-outs.

Endpoints
The primary endpoint for testosterone suppression was the onset and the duration of the testosterone suppression below the castration level of 0.5 ng/ml. Moreover, the pharmacodynamic profile of the formulations was studied in terms of testosterone suppression as a surrogate of therapeutic efficacy in advanced prostatic cancer. Testosterone suppression is directly related to therapeutic efficacy. Two administrations 4 weeks apart were planned in order to be able to observe the main variable testosterone suppression below castrate level.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
The following parameters were evaluated and are presented in the table below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{\text{first}}$</td>
<td>Time to onset of castrate level was defined as the time from first administration to the first testosterone value $\leq 0.5$ ng/ml.</td>
</tr>
<tr>
<td>$T_w$</td>
<td>Duration of testosterone suppression. The time during which the concentrations C(t) remained below the castration level (0.5 ng/ml) was calculated.</td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>Maximum stimulated testosterone level. The highest testosterone concentration determined within 6 weeks after first administration for a subject was reported as $C_{\text{max}}$.</td>
</tr>
<tr>
<td>$t_{\text{max}}$</td>
<td>The time at which $C_{\text{max}}$ occurred was reported as $t_{\text{max}}$.</td>
</tr>
<tr>
<td>AUC testosterone</td>
<td>Area under the concentration-time curve of testosterone in the interval of 21 days after administration was calculated by trapezoidal integration ($\text{AUC}_{0-21d}$).</td>
</tr>
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</table>
Table 1  Testosterone-response after Leuprorelin application

<table>
<thead>
<tr>
<th>Treatm.</th>
<th>Stat.</th>
<th>AUC_{0-21}</th>
<th>C_{max}</th>
<th>t_{max}</th>
<th>t_{first} (C_t \leq 0.5)</th>
<th>T_w (C_t \leq 0.5)</th>
<th>t_{last} (C_t \leq 0.5)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>ng/ml d</td>
<td>ng/ml</td>
<td>d</td>
<td>d</td>
<td>d</td>
<td>d</td>
</tr>
<tr>
<td>A</td>
<td>N</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>92.63</td>
<td>10.14</td>
<td>3.85</td>
<td>23.35</td>
<td>55.87</td>
<td>77.78</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>21.14</td>
<td>2.71</td>
<td>1.56</td>
<td>5.21</td>
<td>6.51</td>
<td>4.41</td>
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<tr>
<td></td>
<td>Min</td>
<td>52.80</td>
<td>5.75</td>
<td>1.98</td>
<td>10.98</td>
<td>37.23</td>
<td>69.99</td>
</tr>
<tr>
<td></td>
<td>Med</td>
<td>97.76</td>
<td>10.10</td>
<td>3.50</td>
<td>23.00</td>
<td>56.51</td>
<td>77.00</td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>131.13</td>
<td>15.76</td>
<td>6.99</td>
<td>33.99</td>
<td>65.02</td>
<td>84.03</td>
</tr>
<tr>
<td></td>
<td>GeoM</td>
<td>90.06</td>
<td>9.80</td>
<td>3.95</td>
<td>22.72</td>
<td>55.46</td>
<td>77.67</td>
</tr>
<tr>
<td></td>
<td>G_CV</td>
<td>26.2</td>
<td>28.0</td>
<td>39.7</td>
<td>26.0</td>
<td>13.2</td>
<td>5.7</td>
</tr>
<tr>
<td>B</td>
<td>N</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>74.24</td>
<td>7.73</td>
<td>2.83</td>
<td>22.53</td>
<td>51.05</td>
<td>71.17</td>
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<tr>
<td></td>
<td>SD</td>
<td>14.67</td>
<td>1.36</td>
<td>1.72</td>
<td>4.08</td>
<td>13.78</td>
<td>9.30</td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>53.71</td>
<td>6.11</td>
<td>1.00</td>
<td>17.98</td>
<td>24.99</td>
<td>56.00</td>
</tr>
<tr>
<td></td>
<td>Med</td>
<td>75.16</td>
<td>7.47</td>
<td>2.50</td>
<td>22.99</td>
<td>54.29</td>
<td>70.00</td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>91.48</td>
<td>9.29</td>
<td>6.01</td>
<td>27.98</td>
<td>65.49</td>
<td>83.99</td>
</tr>
<tr>
<td></td>
<td>GeoM</td>
<td>72.98</td>
<td>7.63</td>
<td>2.45</td>
<td>22.22</td>
<td>48.98</td>
<td>70.64</td>
</tr>
<tr>
<td></td>
<td>G_CV</td>
<td>20.8</td>
<td>17.7</td>
<td>65.2</td>
<td>18.5</td>
<td>35.2</td>
<td>13.6</td>
</tr>
</tbody>
</table>

In spite of the differences of total leuprorelin exposure between treatments, the clinically relevant parameters of efficacy, the onset of the castration level and the duration of testosterone suppression, did not differ between the formulations.

The action of leuprorelin on testosterone is biphasic as a transient increase is followed by testosterone suppression. The pharmacodynamic variables that reflect the acute action - AUC, C_{max} and t_{max} - were determined for a time interval of 21 days after the first application, respectively. After the second application the acute testosterone response was negligible. The re-increase of the testosterone concentrations (t_{last} (C_t \leq 0.5)) that was observed 77.78 d after treatment a and 71.17 d after b do not reflect any longer a leuprorelin action but are indicating the end of it.

Four days after application of treatment a a testosterone mean concentration reached a maximum of 9.40 ng/ml. For treatment B a maximum of 7.14 ng/ml was observed 3 days after application.

Twenty-two days after the first application of both formulations the testosterone concentrations had dropped to values below the castration level of 0.5 ng/ml in half of the subjects and latest 28 days after the reference and 34 days after test in all subjects. Point estimator and 90% CI for the difference of medians was 0.01d (-3.99 d - 3.99 d).

The acute testosterone response in terms of AUC_{0-21 (d)} (geometric means: A = 90.06 ng/ml d, B = 72.98 ng/ml d), C_{max} (geometric means: A = 9.80 ng/ml, B = 7.63 ng/ml) and t_{max} (medians: A = 3.50 d, B = 2.50 d) indicate minor differences between treatments with respect to testosterone response.

The parameters reflecting testosterone suppression were, however, comparable between treatments. The onset of the castration level was reported as the time point when the testosterone concentration dropped below the castration level for the first time after the first leuprorelin application (t_{first} (C_t \leq 0.5 ng/ml)). The median of t_{first} (C_t \leq 0.5 ng/ml) amounted to approximately 23 days after both treatments. The duration of testosterone suppression was (55.87 d) slightly longer after test than after the reference (51.05 d) (ns). The point estimator and the 90% CI for the difference of the expected medians amounted to 4.82d (CI -2.90d - 12.54d). The variability of the duration of the testosterone suppression after the test formulation (CV=11.7%) was considerably lower than after the reference (CV= 27.0%). In one subject receiving the reference the duration of testosterone suppression was only 25 days, i.e., slightly shorter than the dosage interval. In both application intervals testosterone levels returned precociously to values above the castration level. Under clinical conditions testosterone suppression would have been inadequate in this subject.

The AUC_{0-21} ratio (A/B: 123.4%, 100.4% - 151.7%) shows a significant (Poona-sided <0.05) higher testosterone response for treatment A. This is also true for the rate characteristic C_{max} (128.4%, 103.9% - 158.8%). The calculated CVs for both characteristics with 24.8% and 25.5% were moderate. After both
treatments the testosterone peak concentrations occurred, however, at similar times. The $t_{\text{max}}$ difference was about 1 day (0.99 d, CI -0.01 d - 2.00 d).

The most important feature with respect to efficacy is the duration of testosterone suppression in terms of $(T_w (C_t \leq 0.5))$ for which both treatments were comparable the difference amounting to 4.82 d (CI -2.90 d - 12.54 d), indicating a slight superiority of treatment A in comparison to treatment B (ns). Likewise, the onset of testosterone suppression $t_{\text{first}} (C_t < 0.5)$ did not differ between the treatments (A-B: 0.01 d, CI 3.99d - 3.99 d). On day 28 before the second application 13/14 subjects after treatment A (93%) and 5 of 6 subjects (83%) after treatment B exhibited concentrations below 0.5 ng/ml. In all subjects this had happened 34 days (A) and 28 days (B) after the first application. At the end of the second dosage interval on day 56 the testosterone concentrations of all 20 subjects were suppressed below the castration level.

Four weeks later, on day 84, still 4 of 14 subjects receiving treatment A (29%) and 1/6 subjects receiving treatment B (17%) was suppressed below the castration level of 0.5 ng/ml.

**Conclusion**

The differences between the test and reference product with respect to the extent and rate of leuprorelin exposure translate into a minor difference with respect to the initial testosterone flush. However, in spite of the differences of total leuprorelin and testosterone exposure between the treatments, the clinically relevant parameters of efficacy, i.e., the onset of the castration level and the duration of testosterone suppression, did not differ between the formulations.

The duration of testosterone suppression after the test formulation (55.87 d) was slightly longer than after the reference formulation (51.05 d), but the difference was not significant. Both treatments suppressed the endogenous testosterone below the castration level of 0.5 ng/ml and showed approximately comparable concentration-time profiles of this parameter.

Testosterone suppression below castration level is a valid surrogate parameter for the therapeutic efficacy and the mechanism of action of leuprorelin. It is justified from the data provided to predict that the newly developed leuprorelin implant will be as efficacious under therapeutic conditions as Enantone®.

**HEX 2: Study 2002-18-IMP-3**

**Design**

Study HEX 2 was designed as a randomized, open label, multicenter, phase III study on pharmacokinetics, pharmacodynamics, efficacy and safety of leuprorelin implant in patients with advanced prostatic cancer in comparison to Enantone®. The implant was applied on 30 patients at 4 consecutive applications every 28 days; 33 patients received 4 consecutive Enantone applications every 28 days. A total of 55 subjects completed the study: 25 on implant and 29 on Enantone subcutaneous injection.

Treatment naive subjects with histologically confirmed, advanced adenocarcinoma of the prostate, stage $T_{3-4}N_0M_0$, $T_{1-4}N_1M_0$ or $T_{1-4}N_0-1M_1$, were enrolled, either as newly (within the past 4 weeks) diagnosed adenocarcinoma of the prostate, or recurrence of adenocarcinoma of the prostate after previous prostatectomy and/or radiotherapy and/or brachytherapy. ECOG Performance status had to be 0-2. Acceptable exclusion criteria were laid down. Anti-neoplastic treatment other than study medication was strictly prohibited during the study. If a subject required such treatment, the subject was to be excluded from the analysis at the investigator's discretion but could remain in the study. The status of prostatic cancer was similar for both treatment groups at screening.

**Objectives**

The 2 primary objectives were defined as follows:

- Proportion of patients with successful testosterone suppression, defined as testosterone levels of $\leq 0.5 \text{ ng/mL}$ for at least 2 consecutive samples within 8 weeks after the first administration and continuing thereafter up to 8 weeks after the first administration; except for escapes and

- Proportion of patients with a testosterone level $\leq 0.5 \text{ ng/mL}$ until week 16: defined as testosterone level $\leq 0.5 \text{ ng/mL}$ at week 16 after having been successfully suppressed within the first 8 weeks after the first administration and remaining below $\leq 0.5 \text{ ng/mL}$ up to week 16, except for escapes.

The secondary objectives of the study were to compare the efficacy measured by the DRE (prostatic status), endocrine response, pharmacokinetics and safety of Leuprorelin Sandoz implant and Enantone®.
The following issues were recorded from the DRE (visit 0, final visit): surface of prostate, rectum mobile over the prostate and the normal prostate size. Prostatic status was based on the results of the DRE and was classified into 4 categories:

1. Returned to normal
2. >50% improved
3. Similar to baseline
4. >25% worsened

Safety endpoints included:
- Incidence and severity of all adverse events (AEs);
- Incidence and severity of drug related AEs;
- Incidence and severity of local skin reactions at the injection site (e.g. erythema, swelling, tenderness to touch, itching, pain);
- Serious adverse events (SAEs);
- Safety laboratory (haematology, chemistry, urinalysis);
- Need for anti-androgens because of flare symptoms;
- Vital signs (blood pressure, pulse rate, weight);
- Overall tolerability as judged by the investigator and the patient.

Analytical/statistical methods
A safety population (including all subjects who received study medication), an efficacy population (excluding any subjects who had received previous or concurrent medication for prostatic cancer, with the exception of medication for distal bone metastases) were defined. Analysis of efficacy was based primarily on the PP population with an additional analysis on the ITT population.

Efficacy results
Testosterone
The proportion of patients with successful testosterone suppression within 8 weeks was as follows:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Number of patients (%)</th>
<th>Lower bound of the 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Successful</td>
<td>Unsuccessful</td>
</tr>
<tr>
<td>Leuproleline Sandoz depot 1 maand</td>
<td>26</td>
<td>25 (96%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Enantone®</td>
<td>29</td>
<td>25 (86%)</td>
<td>4 (14%)</td>
</tr>
</tbody>
</table>

Due to the small number of patients with unsuccessful suppression, and the relatively small numbers of patients per centre, descriptive results by centre did not show any relevant differences. There were no relevant differences between the treatments in most of the secondary efficacy variables including testosterone levels at various timepoints, time to onset of castration level and duration of suppression.

In both treatment groups, 2 patients had so-called testosterone level escapes. Testosterone level escapes are defined as patients with testosterone levels greater than 0.5 ng/mL for 2 consecutive samples after achieved suppression during 16 weeks under treatment followed by at least one value again ≤ 0.5 ng/mL.

Change in prostatic status (DRE)
Prostatic status of each patient, based on the results of the DREs, was compared from screening visit (visit 0) to the final visit.
As shown in the table below, the proportion of patients who returned to normal was slightly higher in the Leuproleline implant group than in the Enantone group, while the proportion of patients with >50% improvement was approximately 17% higher in the Enantone group compared to the Leupro 1M Sandoz group:

**Change in prostatic status (DRE) compared to screening (PP population)**

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Visit/Week</th>
<th>N (missing)</th>
<th>Number of patients (%)</th>
<th>Returned to normal</th>
<th>&gt;50% improvement</th>
<th>Similar to baseline</th>
<th>&gt;25% worsened</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leuproleline implant</td>
<td>Final</td>
<td>26 (0)</td>
<td>3 (12%) 9 (35%)</td>
<td>12 (46%)</td>
<td>2 (8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enantone®</td>
<td>Final</td>
<td>29 (0)</td>
<td>2 (7%) 15 (52%)</td>
<td>12 (41%)</td>
<td>0 (-)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Change in serum PSA and PAP**
Median concentrations of serum PAP declined after baseline in both groups. The profiles of decline in serum PSA concentration post-baseline were similar in both treatment groups.

**Subjective response on the basis of ECOG performance scale**
ECOG performance status, indicating the general health and mobility of the patient, declined only in one patient in the Leupro 1M Sandoz group (1506) and in 2 in the Enantone® group (1205 and 1206) between baseline and the final visit. The large majority of patients remained at their baseline score and 81% of the Leuproleline implant group and 83% of the Enantone® group were "Able to carry out all normal activities without restriction".

**Subjective clinical symptoms attributable to prostatic cancer**
Most patients 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.

**Overall efficacy as judged by the investigator and patient**
More than 92% of investigators and patients rated the overall efficacy of Leupro 1M Sandoz as good or very good at the final visit and 100% of investigators and patients rated the overall efficacy of Enantone® as good or very good at the final visit.

Efficacy in 2 patients of the Leuproleline implant group was judged by the investigator as "bad", due to a worsening of the tumour of more than 25% in these 2 patients even though the testosterone suppression was successful in both patients.

**Safety results**
All 63 randomized and treated patients (ITT population) were evaluated for safety: 32 treated with Leuproleline implant and 31 with Enantone®. The overall reporting of adverse events (AEs) during the treatment phase was similar for both treatment groups (Treatment Emergent adverse events – TEAEs: 8/32, 25% of the Leuproleline implant patients with 15 TEAEs; 9/31, 29% of the Enantone® patients with 11 TEAEs).
Treatment emergent adverse events (TEAEs) are specified below:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of patients with respective number of AEs</th>
<th>N</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leuproreline implant</td>
<td>32</td>
<td></td>
<td>24 (75%)</td>
<td>5 (16%)</td>
<td>1 (3%)</td>
<td>-</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Enantone®</td>
<td>31</td>
<td></td>
<td>22 (71%)</td>
<td>8 (26%)</td>
<td>-</td>
<td>1 (3%)</td>
<td>-</td>
</tr>
</tbody>
</table>

There were no medically relevant differences for the most common body systems with TEAEs between the 2 treatment groups. The incidence of TEAEs was similar in the 2 treatment groups for events of mild and moderate severity (7/32, 22% of the Leupro 1M Sandoz patients; 8/31, 26% of the Enantone® patients). Two patients in the Leupro 1M Sandoz group had severe TEAEs: one patient with urinary retention (twice, initially unrelated followed by a later episode considered possibly related) and another with bronchopneumonia and heart failure (both were considered unrelated). One patient in the Enantone® group had a severe TEAE (bone pain), but was considered to be unrelated to study medication.

**Conclusion**

The study demonstrated an efficacy of Leuproreline implant at least similar to that of Enantone® in the palliative treatment of advanced prostatic cancer. Leupro 1M Sandoz showed a higher rate of successful testosterone suppression within 8 weeks and continuing thereafter until week 16 than Enantone®, these differences were not statistically significant.

In the PP population, 96% of the patients receiving Leupro 1M Sandoz and 86% of Enantone® patients had successful testosterone suppression within the first 8 weeks. In particular, one patient in the Leupro 1M Sandoz group and 4 patients in the Enantone® group have to be regarded as medical failures, as they were either never suppressed or the suppression lasted insufficiently long. Four months after the application, 85% of the Leupro 1M Sandoz patients and 79% of the Enantone® patients were still suppressed.

There were no relevant differences between the treatments in most of the secondary efficacy variables including testosterone levels at various timepoints, time to onset of castration level, duration of suppression, prostatic status (DRE), change in serum PSA and PAP, subjective response on the basis of ECOG performance scale, subjective clinical symptoms attributable to prostatic cancer (dysuria, nocturia, bone pain), overall efficacy as judged by the investigator and the patient and endocrine response. There were 2 patients with testosterone escapes in the Leupro 1M Sandoz group and 2 patients with escapes in the Enantone® group.

Objectives of efficacy were reached.

Patients in both treatment groups experienced a comparable number of TEAEs and the majority of these were mild or moderate in intensity. One Leupro 1M Sandoz patient died due to pneumonia and heart failure. The death was considered to be unrelated to the study medication. No patient discontinued the study due to TEAEs. No clinically relevant changes in laboratory parameters or vital signs were noted in either treatment group during the study. Both treatments were therefore comparable with respect to local and systemic tolerance.

Both treatments were equally safe and well tolerated.

**HEX 3: Study 2002-19-IMP-4**

**Design**

Study HEX3 was an open label, single arm multicenter, phase II study on pharmacokinetics, efficacy and safety of leuprorelin implant in patients with advanced prostatic cancer. Twenty patients received 4 consecutive applications every 28 days. All subject completed the study. Patients with newly diagnosed or recurrent, histologically confirmed, advanced adenocarcinoma of the prostate, stage T3aN0M0, T1aN1M0 or T1bN0,M1, were enrolled in this study.
Efficacy variables
The primary efficacy variables were:
- Proportion of patients with successful testosterone suppression within 8 weeks,
- Proportion of patients with a testosterone level of $\leq 0.5$ ng/mL until week 16.
The secondary variables of the study were a.o. endocrine response and safety of Leuprorelin Sandoz implant.

Primary efficacy results
Proportion of patients with successful testosterone suppression within 8 weeks
All 20 patients treated with Leupro 1M Sandoz achieved and maintained successful testosterone suppression (2 consecutive testosterone levels $\leq 0.5$ ng/mL) within 8 weeks of administration.

Proportion of patients with successful testosterone suppression within 8 weeks (PP population)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Number of patients (%)</th>
<th>Lower bound of the 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leupro 1M Sandoz</td>
<td>20</td>
<td>20 (100%)</td>
<td>86.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

Proportion of patients with successful testosterone suppression until week 16
The testosterone values of all patients who were successfully suppressed within the first 8 weeks still remained below the castration level of $\leq 0.5$ ng/mL until week 16 (at the end of the fourth dosing interval).

Secondary efficacy results
No patient had an escape in testosterone level. No patients had worsened prostatic status measured by digital rectal examination. The majority of patients also showed stable or improved subjective response on the basis of ECOG performance scale and severity of the clinical symptoms dysuria, nycturia and bone pain. Median concentrations of prostatic acid phosphatase (PAP) and prostate specific antigen (PSA) declined towards normal range after baseline, PSA concentrations were 12.70 ng/mL lower at the final visit compared to baseline.

Safety results
Leupro 1M Sandoz was safe and well tolerated in patients with advanced prostatic cancer in this study. Patients were exposed to leuprorelin for 16 weeks. During the study, no deaths occurred and no SAEs were reported. No patients discontinued from the study due to treatment emergent AEs (TEAEs). Seventeen of the 20 patients (85%) reported a total of 25 TEAEs. All of the TEAEs were either mild or moderate in severity. The most common TEAEs reported were hot flushes. Twelve (60%) patients reported TEAEs that were possibly related to the study drug, of which hot flushes was again the most common event. One patient had a mild reaction at the injection site that did not require any treatment and resolved completely.
There were no clinically relevant changes in laboratory parameters or vital signs during the study.

Conclusion
All patients for whom a definite efficacy assessment was possible were successfully suppressed within 8 weeks of administration and remained below the castration level of 0.5 ng/mL until week 16 (end of study). The median time to onset of the castration level was 26 days and the median duration of suppression was 86 days, corresponding to about 3 months. Thus, patients remained suppressed within each dosing interval from the second application on, and the treatment goal of suppression until the next dosing was achieved.

Design
The aim of this meta-analysis of pooled data from 2 studies on Leupro 1M Sandoz (2002-18-IMP-3 and 2002-19-IMP-4), was to further investigate the pharmacokinetics, pharmacodynamics, efficacy and safety of Leupro 1M Sandoz in larger numbers of patients with advanced prostatic cancer and to compare the results to those obtained for the approved drug Enantone® in study 2002-18-IMP-3. The primary objectives of the study focused on pharmacodynamics in terms of testosterone suppression, as this is a valid surrogate parameter for the clinical efficacy of this kind of treatment for prostatic cancer. Results of the 2 studies, as well as complete information on their conduct, can be found in the individual study reports above.
Pooling of the data from both studies was possible, since the inclusion and exclusion criteria were identical in both studies as were the specific study procedures.

Study populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Number of patients (patient no.)</th>
<th>Leupro 1M Sandoz</th>
<th>Enantone®</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screened</strong></td>
<td></td>
<td></td>
<td></td>
<td>107</td>
</tr>
<tr>
<td>Randomized</td>
<td>52</td>
<td>31</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td><strong>Safety population</strong> (received study medication)</td>
<td>52</td>
<td>31</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td><strong>Switch of study medication group due to an application mistake</strong></td>
<td>-2</td>
<td>+2</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>ITT population</strong></td>
<td>50</td>
<td>33</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Application failure</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Lack of sufficient data</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Wrong medication</td>
<td>-</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>PP population</strong></td>
<td>46</td>
<td>29</td>
<td>75</td>
<td></td>
</tr>
</tbody>
</table>

Primary efficacy variables
The main population used for the analysis of efficacy was the PP population. The results for the PP and ITT populations were similar. Therefore, the results for the PP population are presented and discussed below.

Proportion of patients with successful testosterone suppression within 8 weeks
45 of the 46 (98%) patients in the Leupro 1M Sandoz group and 25 of the 29 (86%) patients in the Enantone group achieved and maintained successful testosterone suppression (2 consecutive testosterone levels ≤ 0.5 ng/mL) within 8 weeks of administration. The respective one-sided 95% CIs (Leupro 1M Sandoz: [90.1%; 100%] and Enantone® [71.2%; 100%]) indicate a slightly higher success rate for Leupro 1M Sandoz than for Enantone®.
Proportion of patients with successful testosterone suppression within 8 weeks (PP population)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Number of patients (%)</th>
<th>Lower bound of the 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Successful</td>
<td>Unsuccessful</td>
</tr>
<tr>
<td>Leupro 1M Sandoz</td>
<td>46</td>
<td>45 (98%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Enantone®</td>
<td>29</td>
<td>25 (86%)</td>
<td>4 (14%)</td>
</tr>
</tbody>
</table>

Secondary efficacy variables

All secondary efficacy variables were only described for the PP population. There were no relevant differences between the treatments in most of the secondary efficacy variables including testosterone levels at weeks 4, 8, 12 and 16, change in serum PSA and PAP, subjective response on the basis of ECOG performance scale, subjective clinical symptoms attributable to prostatic cancer (dysuria, nycturia, bone pain), overall efficacy as judged by the investigator and the patient, and endocrine response. The proportion of patients who returned to normal was slightly higher in the Leupro 1M Sandoz group (11%) than in the Enantone® group (7%) while the proportion of patients with >50% improvement was similar in both treatment groups. The incidence of escapes was similar for both treatment groups (Leupro 1M Sandoz: 2 and Enantone®: 2).

The extent of initial testosterone flush was slightly higher after Leupro 1M Sandoz application. The median time to onset of castration level was similar in both groups (Leupro 1M Sandoz 28 days and Enantone® 27 days); the ranges were broad for both treatments and widely overlapping. The median duration of suppression was 86 days for both treatment groups, corresponding to about 3 months.

No clinically relevant difference with respect to efficacy was found.

Safety results

One Leupro 1M Sandoz patient died due to pneumonia and heart failure. Altogether, 2 patients had SAEs: the one Leupro 1M Sandoz patient who died and one Enantone® patient who was hospitalized for pneumonia. Neither of these SAEs was considered to be related to study medication. Patients in both treatment groups were exposed to study medication for approximately 16 weeks and had a comparable incidence of TEAEs, with the exception of a slightly higher incidence of hot flushes in the Leupro 1M Sandoz group. The majority of these events were mild or moderate in severity. One Leupro 1M Sandoz patient had a mild reaction at the injection site that did not require any treatment and resolved completely.

There were no clinically relevant changes in laboratory parameters or vital signs in either treatment group during the study. Overall, there was no clinically relevant difference in safety profile.

Overall conclusion

Three studies and one meta-analysis were reported. The studies sufficiently demonstrated the Sandoz implant (3.5 mg) suppressed endogenous testosterone below the castration level. There were no relevant differences between the treatments in most of the secondary efficacy variables including testosterone levels at various timepoints, time to onset of castration level, duration of suppression, prostatic status (DRE), change in serum PSA and PAP, subjective response on the basis of ECOG performance scale, subjective clinical symptoms attributable to prostatic cancer (dysuria, nycturia, bone pain), overall efficacy as judged by the investigator and the patient and endocrine response.

No relevant differences in incidence or pattern of AEs are observed between the two treatments investigated.

Both treatments are safe and well tolerated, there is no relevant difference in safety profile.

Risk management plan

The safety profile of leuprolelin 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 similar product Leuproleline Sandoz depot 5 mg implant (NL RVG 30594), which has been previously approved.

**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 1 maand 3.6 mg, implant has a proven chemical-pharmaceutical quality and is a legitimate hybrid form of Lucrin Depot leuprorelin acetate 3.75 mg, powder 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 3.6 mg, the product is a biodegradable implant containing 3.6 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. 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 essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Leuproreline Sandoz depot 1 maand 3.6 mg, implant was authorised in the Netherlands on 9 January 2009.

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

AE  Adverse Event
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
Cmax  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
ECOG  Eastern Cooperative Oncology Group
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
ITT  Intent-to-treat
MAH  Marketing Authorisation Holder
MEB  Medicines Evaluation Board in the Netherlands
OTC  Over The Counter (to be supplied without prescription)
PAP  Prostatic Acid Phosphatase
PAR  Public Assessment Report
Ph.Eur.  European Pharmacopoeia
PIL  Package Leaflet
PP  Per-protocol
PSA  Prostate Specific Antigen
PSUR  Periodic Safety Update Report
SAE  Serious Adverse Event
SD  Standard Deviation
SPC  Summary of Product Characteristics
t½  Half-life
tmax  Time for maximum concentration
TEAE  Treatment Emergent Adverse Event
TSE  Transmissible Spongiform Encephalopathy
USP  Pharmacopoeia in the United States
### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfer of marketing authorisation</td>
<td>--</td>
<td>MA transfer</td>
<td>14-12-2009</td>
<td>23-2-2010</td>
<td>Approval</td>
<td>N</td>
</tr>
<tr>
<td>Change in the qualitative and/or quantitative composition of the immediate packaging material.</td>
<td>--</td>
<td>IB</td>
<td>14-12-2009</td>
<td>18-1-2010</td>
<td>Approval</td>
<td>N</td>
</tr>
<tr>
<td>Submission of a new or updated Ph. Eur. certificate of suitability; For an active substance, European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph; updated certificate from an already approved manufacturer.</td>
<td>--</td>
<td>IA</td>
<td>16-12-2010</td>
<td>18-12-2010</td>
<td>Approval</td>
<td>N</td>
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</tbody>
</table>