Public Assessment Report
Scientific discussion

Lutrate Depot 3.75 mg
powder and solvent for prolonged-release suspension for injection
(Leuprorelin acetate)
Registration number in Spain: 74980

EU-procedure number:
ES/H/0141/001/DC

Applicant: Gp-Pharm, S.A

This module reflects the scientific discussion for the approval of Lutrate Depot 3.75 mg. The procedure was finalised on 6 September 2011. For information on changes after this date please refer to the module 'Update'.

INTRODUCTION

Lutrate Depot 3.75 mg powder and solvent for prolonged-release suspension for injection was originally approved in 6th September 2011 via the decentralised procedure ES/H/0141/001/DC.
A repeat-use mutual recognition procedure, ES/H/0141/001/E/001, was finalised in May 2012. During the repeat-use procedure, the MAH committed to update the product information as requested by the new CMS. Accordingly, the MAH submitted a type II variation to implement the changes agreed on during the repeat-use procedure.

This marketing authorisation application is submitted in accordance with article 8.3 of Directive 2001/83/EC, as amended, so called "complete and independent application", for a known active substance.

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for **Lutrate Depot 3.75 mg powder and solvent for prolonged-release suspension for injection** in the palliative treatment of advanced prostate cancer, is approvable.

EXECUTIVE SUMMARY

Problem statement

Prostate cancer (PCa) is recognized as one of the most important medical problems facing the male population. In Europe, PCa is the most common solid neoplasm, with an incidence rate of 214 cases per 1000 men, outnumbering lung and colorectal cancer. Furthermore, PCa is currently the second most common cause of cancer death in men.

Clinically localised PCa is a potentially curable disease in the majority of men. The standard treatment for patients with localised disease (T1-2, N0/X, M0/X) is definitive local therapy (radical prostatectomy (RP) or radical radiotherapy, RT).

For patients with locally advanced disease (T3, N0/X, M0/X), the primary treatment options are either RT with adjuvant androgen deprivation therapy (ADT) or alternatively RP with adjuvant RT.

Androgen deprivation therapy (ADT) is considered the current standard of care in men with advanced prostate cancer (T4, N0, M0; any T, N1, MO; any T, any N, M1). It may take the form of surgical castration (bilateral orchiectomy) or chemical castration, for which a variety of agents have been used. Long-acting GnRH agonists, such as leuprorelin, goserelin, triptorelin, buserelin and histrelin, are most widely used although pure GnRH antagonists have also been developed. ADT is palliative and not curative. It can normalize serum levels of PSA and can produce objective tumor response. This antitumor activity can improve QoL by reducing bone pain and complications such as spinal cord compression and ureteral obstruction. It remains unclear whether or not overall survival is prolonged.

GnRH agonists are currently delivered as depot injections on a one-, three- or six-monthly basis. There is no evidence that any of the GnRH analogues differs with respect to efficacy and safety.

About the product

GP-Pharm has developed a new depot leuprorelin formulation to be administerd IM on a one-monthly basis. The mechanism of action of leuprorelin is the same as other GnRH analogs: down-regulation of GnRH receptor number and post-receptor desensitization in gonadotropic cells, which leads to a decrease in LH and FSH secretion and suppression cellular response to endogenous GnRH. The end result is a suppression of testicular or ovarian steroidogenesis.

The Pharmacotherapeutic group is "Gonadotropin releasing hormone analogues" and the ATC code is L02AE02.

The active substance, Leuprorelin, is a well known GnRH agonist, which has been available for use in clinical practice for more than twenty years. The proposed indication is the treatment of hormone-dependent prostate cancer.

Lutrate Depot is a new sustained-release formulation of microencapsulated leuprorelin acetate. The delivery system consists of a biodegradable polymer of lactic-glycolide, and the release is modulated by triethyl citrate. The formulation is to be injected intramuscularly monthly.

General comments on the submitted dossier

GP-Pharm S.A has submitted via the Decentralised Procedure an application for a marketing authorisation for **Lutrate Depot 3.75 mg powder and solvent for prolonged-release suspension for injection**, which contains leuprorelin acetate, with Spain acting as Reference Member State. Concerned Member States are Germany, Greece, Italy and Portugal.
In addition, a repeat-use mutual recognition procedure, ES/H/0141/001/E/001, was submitted, with Spain acting as Reference Member State and Concerned Member States are AT, BE, BG, CZ, DK, EE, FI, HU, IE, LT, LV, NL, NO, PL, RO, SE, SK and UK.

In both procedures, the marketing authorisation application was submitted in accordance with article 8.3 of Directive 2001/83/EC, as amended, so called "complete and independent application", for a known active substance.

There is no paediatric development programme for Lutrate Depot. The Applicant has submitted the confirmation by the EMA of the applicability of the Decision on a class waiver for products intended for the treatment of prostate carcinoma to Lutrate Depot.

Scientific Advice was given by the Spanish Agency for Medicines and Healthcare Products on April 2007 and September 2008.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The Applicant states that all the studies were performed in accordance with the relevant guidelines of the Declaration of Helsinki and according to the general principles of: "ICH Harmonized Tripartite Guidelines for Good Clinical Practice" ICH Topic E6.

An ordinary GCP inspection has been carried out for this procedure. Some centers of the main study have been inspected coinciding with the clock-stop period (after Day 105). The inspection was conducted following a request from the Clinical Evaluation Department of the General Deputy of Medicines for Human Use of the AEMPS in connection with their evaluation of the MAA for Lutrate. The purpose of the inspections was to verify whether the clinical trials were conducted in compliance with GCP and applicable regulations in particular where it has impact on the validity of the data or the ethical conduct of the trials.

The conclusion of the inspections was the following:

Data obtained at the sites inspected are considered reliable and can be acceptable as a basis of the marketing authorisation application.

With regards to Good Laboratory Practice (GLP), the Applicant declares that the toxicological studies were conducted according to Good Laboratory Practice (GLP) standards. No information about GLP status of bibliographical studies is provided, however given the development of leuprorelin 20 years ago, the non-clinical studies predate the introduction of GLP and it is very unlikely that they were conducted to current standards.

SCIENTIFIC OVERVIEW AND DISCUSSION

II-1 Quality aspects

Active substance

Leuprorelin is a known active substance described in Ph. Eur. A Ph. Eur. Certificate of Suitability has been submitted to support the quality of the active ingredient.
The CEP does not include re-test period but stability data have been included in the dossier to support the proposed the re-test period.

Finished product

Description of the product
Lutrate Depot 3.75 mg powder and solvent for prolonged-release suspension for injection is provided as a powder for suspension for injection intended for reconstitution with mannitol 0.8% to form a suspension prior to intramuscular administration.
The qualitative composition of the powder and the solvent are as follows:
Powder:

- Leuprorelin Acetate
- Poly(DL-lactide-coglycolide)
- Triethyl citrate
- Mannitol
- Carmellose sodium
- Polysorbate 80

Solvent:

- Mannitol
- Hydrochloric acid
- Sodium hydroxide
- Water for injection

The powder for suspension for injection is packed in a type I glass vial, hermetically closed with an elastomeric stopper and sealed with a flip-off cap.
The diluent is filled into type I glass syringe closed by an elastomeric stopper.

Pharmaceutical development
The pharmaceutical development has been adequately described.
The function of the key excipients (those modifying release) has been extensively discussed.
An *in vitro* release test has been developed. The data provided support its use and the peptide release specification.

Manufacture of the product and process controls
The manufacturing process is sufficiently described and the process controls are appropriate, considering the nature of the product and the manufacturing method.
The commercial batch size is defined.
The dossier includes sufficient validation data to guarantee that the manufacturing process is controlled and to ensure batch to batch reproducibility and compliance with product specifications.

Excipients
The information provided is adequate. The specifications for the different excipients are justified by their official adoption in the relevant Ph. Eur. monograph or by an in-house monograph (for the non-compendial excipient).

Product specification
The specifications proposed for the powder and the solvent are adequate. The limits proposed for the different parameters have been adequately justified.
The analytical methods have been properly described and validated.

Container closure system
The powder is packaged in Type I glass (Ph. Eur.) vials closed with a elastomeric stopper. The solvent (mannitol 0.8% solution for injection) is packaged in Type I glass syringes designed for packaging and administering medicinal products.
The components of the container closure system comply with the specifications established in the applicable Ph. Eur. monographs.

Stability of the product
The stability studies have been performed following the ICH guidelines. The stability data support the proposed shelf-life and storage conditions.

II-2 Non-clinical aspects

The Applicant relates that the toxicological profile of leuprorelin acetate is extensively known, as reflected in the Toxicology Written Summary (section 2.6.6 of the dossier) and according to these data it was considered that not additional toxicity studies were necessary for Leuprorelin GP Pharm 3.75 mg depot. Following the "Guideline on the Nonclinical documentation for Mixed Marketing Authorisation Applications CPMP/SWP/799/95", the Applicant makes use of the extensive bibliographic references as regards to the pharmacokinetic (PK), pharmacodynamic (PD) and toxicological profile of leuprorelin acetate and presents six non-clinical studies to complete the profile of its leuprorelin depot formulation.

In this assessment report, CHMP/ICH Non-clinical Guidelines have been considered, mainly the CPMP/SWP/799/95 (ICH S6) "Guideline on the Non-clinical documentation for Mixed Marketing Authorisation Applications", the "Note for Guidance on Safety Pharmacology studies for Human Pharmaceuticals CPMP/ICH/539/00 (ICH topic S7A)" and the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human use EMEA/CHMP/SWP/4447/00".
The Applicant declares that the studies were conducted according to Good Laboratory Practice (GLP) standards . No information about GLP status of bibliographical studies is provided, however given the development of leuprorelin 20 years ago, the non-clinical studies predate the introduction of GLP and it is very unlikely that they were conducted to current standards.

Pharmacology

The active ingredient of Lutrate depot 3.75 mg is leuprorelin acetate, a synthetic nonapeptide luteinising hormone-releasing hormone (LHRH) analogue which induces down-regulation of the LHRH receptor and post-receptor desensitisation native human.
Since the safety and efficacy of leuprorelin acetate is well established, all non-clinical studies for Leuprorelin GP Pharm 3.75 mg depot (Lutrate depot) were performed in order to characterize the safety and efficacy profile of the formulation, and to establish the minimum efficacious and safe leuprorelin dose.

Primary pharmacodynamics

The primary and general safety pharmacology of leuprorelin acetate is explained with bibliographical references from 1990, some of which are related to leuprorelin formulations close to GP Pharm development.
Besides this general documentation, six non-clinical studies were conducted by the Applicant to investigate the primary pharmacodynamics Leuprorelin GP-Pharm formulation (Lutrate depot) in male beagle dogs (table 1).

Table 1. Non-clinical studies performed with Leuprorelin GP-Pharm formulation (Lutrate depot).

NON-CLINICAL STUDIES
(RCC 842708) Preliminary PK/PD: Comparison of Leuprorelin GP Pharm 7.5 mg depot vs. Procrin® 7.5 mg (Abbott) in beagle dogs, intramuscular administration.
(CD06/10274FC) Efficacy of two developmental batches: single i.m. administration to male beagle

dogs (n=8) to determine PD (testosterone levels). (Dose used 0.198 mg/kg).
(CD05/9817FC) Efficacy of First clinical batch: single i.m. administration to male beagle dogs (n=4) to determine PD (testosterone levels). (Dose used 0.198 mg/kg).
(S01258) Efficacy of Second clinical batch: single i.m. administration to male beagle dogs (n=4) to determine PD (testosterone levels). (Dose used 0.198 mg/kg).
(S04680) Efficacy of clinical batches (Retest): Due to a slower enrolment for Clinical Trial CRO-04-62, efficacy of clinical batches was retested. Single i.m. administration to male beagle dogs (n=5) to determine PD (testosterone levels). (Dose used 0.200 mg/kg).
(S12565) Efficacy of three Validation batches: single i.m. administration to male beagle dogs (n=9) to determine PD (testosterone levels) and PK (leuprorelin levels). (Dose used 0.200 mg/kg).

In summary the results from these studies showed that castrate levels were achieved by day 7 or 14 and testosterone levels remained below castration levels for the remainder of the sampling period. Castration testosterone levels were maintained up to day 42 after a single i.m. administration.

Additionally the Applicant presented a PK/PD comparative study (*RCC 842708*) in beagle dogs between a 7.5 mg Leuprorelin GP-Pharm formulation and Procrin 7.5 mg depot. to investigate the pharmacokinetic (PK) and the pharmacodynamic (PD) profile of Leuprorelin acetate 7.5 mg depot GP-Pharm formulation. The study consisted of 2 treatment groups with 4 dogs in each. Group 1 received the test article (7.5 mg depot formulation, GP Pharm) and Group 2 received the reference article. Both, the test article and the reference article were administered as a single i.m. dose of 0.3 mg/kg. The observation period lasted 8 weeks.
The GP-Pharm formulation obtained similar results as the marketed product in castration levels. in the majority of the dogs.

Secondary pharmacodynamics and Safety pharmacology

The Applicant comments a study performed in mice, rats and cats treated with 10 mg/kg of subcutaneously administered leuprorelin in which no changes were observed in central and somatic nervous system, cardiovascular system or respiratory system. Furthermore in vitro studies have demonstrated increase and decrease in contractility of various muscle types in guinea pig, rat and rabbit tissue but the study concludes that even at a high dose, leuprorelin acetate was considered not to have notable acute pharmacological actions on the systems evaluated in these tests (Kito and Yoshimura 1990). The results obtained in this study are summarised in table 2.

Table 2. General / safety pharmacology of leuprorelin acetate

Assessment (dose)	**Finding**
General behaviour (mouse: 10 mg/kg)	Slight sedation followed by reduced exploratory behaviour
Spontaneous locomotor activity (mouse:1, 3, 10 mg/kg)	No effect at 1 or 3 mg/kg, decrease at 10 mg/kg
Coordinated movement (mouse: 1, 3, 10 mg/kg)	No effect
Anticonvulsive action (mouse: 1, 3, 10 mg/kg)	Decrease in electric shock convulsion (10 mg/kg only), metrazol convulsion not affected
Pentobarbital sleeping time (mouse: 1, 3, 10 mg/kg)	No effect
Analgesic action (mouse: 1, 3, 10 mg/kg)	No significant effects
Body temperature (rat: 1, 3, 10 mg/kg)	Tendency to significantly increase (3 and 10 mg/kg)
Spontaneous brain waves and behaviour (cat: 10 mg/kg)	No effect
Spinal reflex (cat: 10 mg/kg)	No effect
Cardiovascular and respiratory system (cat: 3, 10 mg/kg)	Slight increase in pulse (10 mg/kg), no effect on respiration, blood pressure or electrocardiogram

	(ECG)
Autonomic nervous system (cat: 10 mg/kg)	No effect on induced bradycardia, pressor reaction, nictitating membrane contraction or blood pressure
Urinary volume and electrolytes (rat: 1, 3, 10 mg/kg)	No significant effects
Digestive system (rat: 1, 3, 10 mg/kg)	No effect on gastric fluid secretion or enteric transport
Anti-inflammatory effects (rat: 1, 3, 10 mg/kg)	No significant effect on carrageenin oedema

Pharmacodynamic drug interactions

Studies addressing pharmacodynamic drug interactions have not been conducted. The lack of pharmacodynamic drug interactions studies is acceptable taking into account that the non-clinical data might be considered superseded by clinical data and no interactions with other medicinal products have been reported with leuprorelin for the last years.

Overall conclusions on Pharmacology

The pharmacodynamic properties of leuprorelin are well known, for this reason the Applicant has provided a detailed bibliographical references list to support the current application, besides the six non-clinical studies conducted by the Applicant to investigate the 3.75 mg Leuprorelin GP-Pharm formulation in male beagle dogs (table 1).

Studies addressing secondary pharmacodynamics, safety pharmacology, and pharmacodynamic drug interactions have not been conducted. The lack of these studies is acceptable and therefore further nonclinical investigations are not required, taking into account that leuprorelin acetate is a well-known active substance and the leuprorelin GP-Pharm formulation is similar to other PLGA microspheres used since 1989 (Enantone 3.75 mg, Takeda Chemical Industries). In addition there are available clinical data about the leuprorelin used that might supersede non-clinical data.

Supporting this application with bibliographical references is acceptable according to the "Guideline on the Non-clinical documentation for Mixed Marketing Authorisation Applications" CPMP/SWP/799/95 (ICH S6).

With regards to the studies performed by the Applicant, they support the PD/PK profile of the drug product.

On the other hand, the comparative study between Leuprorelin GP Pharm 7.5 mg depot and Procrin® 7.5 mg as the reference product, was performed with a higher dose than 3.75 mg (the dose of the requested product Lutrate depot), nevertheless this could be considered acceptable since there are clinical data of marketed products with the same dose (3.75 mg) and with a similar formulation than Lutrate depot. However the final decision about these pharmacodynamic considerations will depend on the clinical assessment.

Pharmacokinetic studies

The Applicant provides a historical data of leuprorelin acetate pharmacokinetics based on bibliographical studies as well as the results from the 6 studies described above.
The report includes a summarized data of absorption, metabolism, distribution and excretion providing bibliographical data of Cmax, AUC, protein binding in plasma, placenta transfer after s.c. injection of radiolabelled leuprorelin acetate, performed on male and female rats and male dogs (Naeshiro et al 1990):

- ✓ ^{14}C leuprorelin acetate peak in the plasma at 15 min

- ✓ Distribution was to the pituitary body, thyroid, lungs, liver and kidneys (peak tissue levels at 15 min to 1 h) followed by gradual decrease to 72 h. However, radioactivity levels remained relatively high in the pituitary body, harderian gland, thyroid and adrenal body.

- ✓ There was a poor migration into blood cells
- ✓ Placental transfer in 20 day pregnant rats (the plasma level was lower than in the dams and the unchanged form was found to be poorly transferred)
- ✓ Both the unchanged drug and some metabolites were found in the milk of lactating rats
- ✓ Protein binding in plasma, as determined *in vitro*, was relatively weak (around 39% [rat], 62% [dog] and 45% [human])
- ✓ There were four identified metabolites. *In vitro* studies indicated formation of the metabolites in a wide range of tissues, except plasma. The main component in the plasma was the unchanged form, and the quantities of the metabolites M-I and M-II were small.
- ✓ Excretion of radioactivity in both rats and dogs occurred initially (at 4 hrs) in the urine with faeces and expired air containing more radioactivity at later time points, such as at 24 and 48 hrs.
- ✓ The excretion rates to urine, faeces, and expired air were respectively about 49%, 22% and 16% of the administered 14C-Leuprorelin acetate in male rats, and 68%, 17% and 12% in dogs. The extent of the enterohepatic circulation of ^{14}C was small.
- ✓ Faecal excretion occurred via the bile
- ✓ No indication of accumulation with continuous administration. Leuprorelin acetate is well absorbed after subcutaneous administration.

In addition, the Applicant provides the pharmacokinetics data from the comparative study (*RCC 842708*) between GP-Pharm 7.5 mg leuprorelin formulation and Procrin 7.5 mg depot previously mentioned in pharmacology section, concluding that given the similar testosterone response observed in both groups the differences in PK are not likely a clinical concern, as the GP-Pharm leuprorelin formulation seems to be as efficacious as the marketed product (dose 7.5 mg). The main results from this study are shown in table 3.

Table 3. Leuprorelin PK parameters from the *RCC842708* study

Leuprorelin 7.5 mg depot formulation	Cmax (pg/mL)	Tmax (hours)	AUC 0-1d (pg x day/mL)	AUC 0-49d (pg x day/mL)	AUC 0-∞ (pg x day/mL)	T½ (days)
GP Pharm (Group 1)	6339	1	1443	10000	10501	11.9
Procrin (Group 2)	37073	1	4349	12021	12305	11.3

Furthermore, the Applicant comments the results from a study performed with Lutrate depot 3.75 mg (*S12565PK*): describing that the curve of leuprorelin showed an initial delivery phase from day 0 to day 3 and after that, the delivery was maintained constant until the end of the study (day 42), and a comparative between this non-clinical study and a clinical study performed in patients with prostate cancer treated with Lutrate Depot 3.5 mg (CRO-04-62). These data showed that plasma testosterone levels below castration level (i.e. testosterone <0.5ng/mL) were achieved on day 28 in both, beagle dogs and patients. In dogs, these levels were achieved one week before (day 14) when compared to the patient group (day 21) (report GP/LP1M/VAL-08-001), Module 4.2).

Pharmacokinetic drug interactions

No pharmacokinetic drug interaction studies were conducted.

The lack of pharmacokinetic drug interactions studies is acceptable taking into account that, as the Applicant claims, leuprorelin is a peptide that is primarily degraded by peptidase and not by

Cytochrome P-450 enzymes, as it was described in several studies and because of the weak binding plasma proteins, drug interactions would not be expected.

Other pharmacokinetic studies

No other pharmacokinetic studies were conducted with Lutrate depot 3.75 mg.

Overall conclusions on pharmacokinetics

According to the "Guideline on the Non-clinical documentation for Mixed Marketing Authorisation Applications" CPMP/SWP/799/95 (ICH S6)", the Applicant claims that considering the known pharmacokinetic profile of leuprorelin acetate and the available data about this in the literature, it is not necessary to perform new studies. However, besides a thorough study as reference (Naeshiro et al 1990) the Applicant presents pharmacokinetics results from two studies (RCC842708 and S12565), performed with leuprorelin GP-Pharm formulation.

From Naeshiro et al study the submitted report provides a review about pharmacokinetics properties of leuprorelin: absortion, distribution, excretion, plasmatic protein binding, isolation and identify of metabolites, Cmax, AUC….

From the studies performed by the Applicant, the report concludes that:

-The comparative study (RCC842708: leuprorelin 7.5 mg GP-Pharm formulation vs. Procrin 7.5 mg) showed that, despite the different Cmax and initial AUC observed between both products, their terminal half life was similar and the Tmax was the same.

-Study S12565PK performed with 3 product batches which showed a similar curve of leuprorelin, with an initial delivery phase from day 0 to day 3 and after that, the delivery was maintained constant until the end of the study (day 42).

-In addition the Applicant comments the results from a comparison between leuprorelin profile in a non-clinical study (S12565PK) and the leuprorelin profile in a clinical study, both studies performed with Lutrate depot 3.75 mg. The leuprorelin release profile was similar in both dogs and patients studies.

Toxicology

The applicant makes use of bibliographic references as regards to the toxicological profile of leuprorelin acetate because it was considered that the toxicological profile of leuprorelin acetate is extensively known and according to these data no additional toxicity studies were necessary for Leuprorelin GP Pharm formulation. This toxicological review is combined with the results from the bioequivalence study performed with Leuprorelin GP-Pharm 7.5 mg depot formulation vs. the marketed reference product Procrin 7.5 mg depot (*RCC 842708*).

Single-dose toxicity

The Applicant relates that the toxicological profile of leuprorelin acetate is extensively known and does not present additional own studies on single-dose toxicity, supporting the current application by presenting bibliographical references.

Due to the Marketing Authorisation Application for Lutrate Depot 3.75 mg is submitted as a Mixed Marketing Authorisation Application as defined in Directive 2001/83, Annex I Part II, 7, the applicant makes use of the Guideline on the Nonclinical documentation for Mixed Marketing Authorisation Applications (CPMP/SWP/799/95) which considers that "Single dose and repeated dose toxicity, as well as local tolerance investigations are normally not necessary" (Section 2 Non-clinical documentation, 2.2 Individual study types, 2.2.1 Single and Repeat-dose Toxicity). Therefore, the absence of single dose toxicity studies is acceptable for this product.

Repeat-dose toxicity

The Applicant relates that the toxicological profile of leuprorelin acetate is extensively known and does not present additional own studies on repeat-dose toxicity, supporting the current application by presenting extensive bibliographical references.

Due to the Marketing Authorisation Application for Lutrate Depot 3.75 mg is submitted as a Mixed Marketing Authorisation Application as defined in Directive 2001/83, Annex I Part II, 7, the applicant makes use of the Guideline on the Nonclinical documentation for Mixed Marketing Authorisation Applications (CPMP/SWP/799/95) which considers that "Single dose and repeated dose toxicity, as well as local tolerance investigations are normally not necessary" (Section 2 Non-clinical documentation, 2.2 Individual study types, 2.2.1 Single and Repeat-dose Toxicity). Therefore, the absence of repeated dose toxicity studies is acceptable for this product.

Genotoxicity

The Applicant has not performed genotoxicity studies with Lutrate Depot 3.75 mg. Nevertheless, the Applicant summarizes several studies from the literature (Fujikawa et al 1990; Sakamoto et al 1990; Nakamura et al 1990) performed with different products of leuprorelin acetate. These studies have shown that leuprorelin acetate provided negative results in genotoxicity or mutagenicity test battery and did not have a chromosome aberration inducing action to CHL (Chinese hamster lung) cells.

Carcinogenicity

No carcinogenicity studies have been performed with Lutrate Depot 3.75 mg. The Applicant provides a bibliographical review about carcinogenicity studies performed with leuprorelin acetate. In these studies pituitary adenomas were observed in rats (24 months repeat dosing), but not in dogs or monkeys (12 months) or in mice (24 months). While there was no histological evidence of pituitary adenoma in the monkey, as with the rat there were increases in pituitary weight. It is necessary to take into account that the 2 year study in the rat is essentially life time, which is not the case for the 12 month study in monkey (Chatani et al 1990; Lupron depot 7.5 mg package 2004).
Additionally in mice, after 2 years dosing, findings of hyperplasia of the pancreatic islet cells and adenomatous polyps in pyloric stomach were reported, but without evidence of carcinogenicity.

As the Applicant claims despite the lack of association between leuprorelin acetate preparations and pituitary adenomas in humans described in several studies, the effects in the pituitary in rats should be considered since indicate that such a reaction in humans may also be possible and a single case of (nodular) hyperplasia of the pituitary gland in man has been reported, whereby an involvement of leuprorelin acetate could not be excluded. Nevertheless, taking into account the therapeutic indication this is not a main concern (Radner et al 1991).

Reproductive and developmental toxicity

The Applicant does not present own reproductive and developmental toxicity studies but provides a brief summary about these aspects based on bibliographical references. It has been described that after leuprorelin acetate treatment, reproduction is adversely affected in animals and there are effects to the foetus (Ooshima et al 1990a-d; Lehrer et al 1992; Lupron depot 7.5 mg package 2004). Additionally adverse effects on erectile function and penile haemodynamics in rabbits and a significant decreased testicular development and steroidogenesis in 7-day old male pigs treated with daily early postnatal administration of leuprorelin acetate, have been observed (Traish et al 2003; Sinclair et al 2001). The reversibility of these negative effects seems to vary according to the animal model, as well as histological lesions after a leuprorelin acetate treatment observed in rats but not in monkeys or dogs, suggesting a species-specific response.

Lutrate Depot 3.75 mg is not indicated in women, therefore further investigations are not required despite the adverse effects with regards to reproduction and developmental, described in the literature.

Local tolerance

The Applicant does not present non clinical studies about local tolerance of Leuprorelin GP-Pharm. formulation but the results of the clinical and the submitted non-clinical toxicological studies performed with a leuprorelin acetate formulation similar to GP-Pharm formulation support the local tolerance of the product

Further investigations are not required, since, besides the available bibliographical data, there is local tolerance information from clinical studies performed with leuprorelin GP-Pharm formulation that did not show unexpected reactions.

Other toxicity studies

Antigenicity

No antigenicity studies have been conducted with Lutrate depot 3.75 mg. From bibliographical data the Applicant refers that no antigenicity was found in a guinea pig active systemic anaphylaxis test and a mouse antibody production test (Nakai et al 1990b).

Immunotoxicity

No immunotoxicity studies have been conducted with Lutrate depot 3.75 mg.

Dependence

No dependence studies have been conducted with Lutrate depot 3.75 mg.

Metabolites

No studies on metabolites have been conducted with Lutrate depot 3.75 mg.
Further investigations are not required since there are available enough data in the literature about the identified metabolites in the leuprorelin acetate metabolism.

Excipients, residual solvents and impurities

The Applicant presents several bibliographical references about the toxicity of lactic and glycolic acids polymers and considers that their toxicity is generally not regarded as a significant issue apart from the local effects that may occur and it is well known that they have been used for several years for drug delivery and in surgical applications without evidence of untoward systemic effects as it has been described in the literature.

There are solvents used during manufacture of the drug product whose residual limits are below the ICH maximum level recommendations. The Applicant provides the residual limits for solvents on the non-clinical overview.

With regards to Triethyl citrate (TEC), the Applicant considers that there are no remarkable concerns arising for the exposure to TEC supporting its argument in several bibliographical references. The Applicant summarizes that TEC was recently recognized as a lower toxicity chemical in the US Federal Register of 2004 and it was considered acceptable like an additive by the FAO/WHO Scientific Committee for Food in 1995. Additionally it is approved by the FDA for food use (GRAS status) and was included in the list of artificial flavouring substances not fully evaluated by the Council of Europe (Opdyke 1979).To complement the information provided in the literature on TEC toxicological profile, the Sponsor conducted three preclinical studies.

- ✓ The first study performed in rats evaluated the potential cumulative toxicity of TEC after daily i.m. administration for a period of 28 days. [Study S27520] The acute toxicity of TEC was also

assessed when administered i.m. at two dose levels followed by an observation period of 27 days. No significant differences between test and control groups were observed in the TEC daily and single administration in any of the parameters evaluated.

- ✓ The second study was to determine the local toxicity of Lutrate depot 3.75 mg vehicle at 3 different doses over a period of 28 days after a single i.m. injection in male NZW rabbits. [Study FCI-10-05-FT]. The lack of significant local toxicity of Lutrate vehicle at the site of injection demonstrated TEC safety profile.
- ✓ The third study evaluated the toxicological profile of TEC when administered i.v. daily to rats for a period of 28 days [Study FCI-08-12-FT]. No physiological significant effect on any of the clinical, biochemical or physical parameters examined was observed.

Additionally, in the PD nonclinical studies conducted, neither local nor general toxicity signs were found in any dog during or after treatment. Furthermore, the injection site reactions with the 1-month formulation administered in 160 patients (6 consecutive monthly injections) were pruritis and urticaria (subsequently quantified in the SmPC as uncommon), with no allergic reactions or sensitization during the follow-up study. By comparison, pruritus and urticaria are considered to be common reactions for other currently marketed leuprorelin depot products not containing TEC.

Impurities pattern

With regards to residual solvents and impurities, the Applicant confirms that the limits are below the ICH maximum level recommendations.

Other studies

No other toxicological studies have been conducted with Lutrate depot 3.75 mg.

Ecotoxicity/environmental risk assessment

The Applicant justifies in Module 1.6 the lack of the environmental risk assessment for Lutrate depot 3.75 mg because of its peptide nature it is unlikely to result in significant risk for the environment.

Overall conclusions on toxicology

The Applicant has provided a brief review of leuprorelin acetate toxicological profile which includes single and repeated-dose toxicity (Chatani et al 1990, Mikoda et al 1990), genotoxicity (Sakamoto et al 1990, Fujikawa et al 1990, Nakamura et al 1990), carcinogenicity (Chatani et al 1990), reproduction and developmental toxicity, local tolerance (Nakai et al 1990, Chatani et al 1990) and antigenicity studies, performed with a similar leuprorelin formulation to the formulation requested in the current application. Besides these studies, the Applicant submits the toxicological results from study RCC 842708. There has not been described that leuprorelin was genotoxic. However, there are enough evidences of adverse effects on reproduction and development caused by leuprorelin and on its carcinogenic potential. Therefore SmPC 5.3 Section reflects this non-clinical information despite Lutrate depot is not indicated in women.

With regards to residual solvents and impurities, the Applicant confirms that the limits are below the ICH maximum level recommendations.

On the other hand, the information provided by the Applicant about TEC administered IM and IV includes non-clinical studies conducted in rats, rabbits and beagle dogs by the Applicant (where neither local nor general toxicity signs were found) and a clinical study performed in 160 patients in which the injection site reactions were pruritis and urticaria, that are considered to be common reactions for currently leuprorelin marketed presentations not containing TEC. No allergic reactions or sensitization during the follow-up study were detected.

II.3 Clinical aspects

Pharmacokinetics

The pharmacokinetic profile of leuprorelin after the IM monthly administration of Lutrate Depot 3.75 mg has been studied in a subgroup of 12 patients from the phase III study in prostate cancer patients (Study CRO 04-62), during the 3 first months of the study (i.eafter 3 repeated doses).

The validated analytical methods for Testosterone and Leuprorelin are deemed acceptable.

Following the first administration, there was a first leuprorelin peak in the first day, followed by a decline in leuprorelin concentration and then by a further increase, starting on 7 day, and a plateau period which is maintained up to day 21.Thereafter plasma levels started to decrease.

The PK profile following the second and third injections were similar to the one described for the first dose. There was no evidence of significant accumulation of leuprolide during repeated dosing.

There were no specific investigations conducted by GP-Pharm relevant to distribution, metabolism or excretion of leuprorelin. However, these data are known from the published data on other leuprorelin products.

Since the indication sought is the treatment of patients with prostate cancer, women and paediatric subjects were not included in the clinical trials. Elderly patients were well represented in the pivotal study in prostate cancer patients. Patients with renal and hepatic impairment have been excluded from clinical trials conducted with Lutrate Depot 3.75 mg. This lack of information has been included in the proposed SPC in section 4.2.and 5.1. Nevertheless, according to data obtained with other marketed formulations containing leuprorelin and other GnRH agonists, increases in leuprorelin concentrations are expected in patients with renal impairment. Despite this fact, due to the wide safety margin of leuprorelin, dose adjustments in patients with impaired renal function are not warranted.

No drug-drug interaction studies have been conducted with Lutrate Depot 3.75 mg. However, because leuprorelin is a peptide that is primarily degraded by peptidase and not by Cytochrome P-450 enzymes, and the drug is only about 46% bound to plasma proteins, drug interactions are not expected to occur.

No drug-drug interactions have been described for other preparations with leuprorelin or other GnRH agonists.

The pharmacokinetic section of the proposed SPC is considered adequate.

A phase I pilot parallel group study was performed in healthy subjects to make a preliminary comparison between Leuprolide GP-Pharm 3.75 mg and 7.5 mg vs the marketed reference products Lucrin 3.75 mg and Procrin 7.5 mg (Abbott)

Table 27 – Leuprolide statistical tests (ANOVA)

Comparison	*Parameter*	*Treatment Effect p-Values*	*90% CI*	*Test result*
T1 vs. R1	C_{max}	*0.026191*	*45.97 – 86.397%*	*BE not established*
T1 vs. R1	AUC_{0-t}	*0.27658*	*81.463 – 245.21%*	*BE not established*
T2 vs. R2	C_{max}	*0.5751*	*59.184 – 131.48%*	*BE not established*
T2 vs. R2	AUC_{0-t}	*0.062116*	*109.66 – 334.55%*	*BE not established*
T1: Leuprolide 3.75 mg deport GP-Pharm *R1: Lucrin® 3.75 mg depot Abbott* *T2: Leuprolide 7.5 mg deport GP-Pharm* *R2: Procrin® 7.5 mg depot Abbott*				

It is clear that the bioequivalence between Leuprolide GP-Pharm vs the marketed reference products cannot be claimed. These formulations give different PK parameters and hence the GP-Pharm product is not considered a generic product of Procrin.

Pharmacodynamics

Leuprorelin is a gonadotropin releasing hormone (GnRH) synthetic analog that shares the action of the naturally occurring hormone. Synthetic GnRH analogs have greater receptor affinity and reduced susceptibility to enzymatic degradation compared to the natural GnRH molecule, and are approximately 100-fold more potent. GnRH agonists bind to the GnRH receptors on pituitary gonadotropin-producing cells, causing an initial release of both luteinizing hormone (LH) and follicle stimulating hormone (FSH), which causes a subsequent increase in testosterone production from testicular Leydig cells. After about one week of therapy, GnRH receptors are down-regulated, with a decline in the pituitary production of LH and FSH. The fall in serum LH leads to a decrease in serum testosterone to castrate levels within three to four weeks after the start of treatment. Continued treatment maintains serum testosterone at castrate levels. The decrease in testosterone production is generally reversible upon cessation of GnRH agonist therapy.

The pharmacodynamic response to Lutrate Depot 3.75 mg, reflected in plasma testosterone concentrations, is consistent with the PD response for other leuprorelin and other GnRH analogs formulations.

Clinical efficacy

The Applicant has conducted a phase III study to support the efficacy and safety of Lutrate Depot 3.75 mg in patients with prostate cancer (Study CRO-04-62). It was an open-label, non-comparative study. Lutrate Depot 3.75 mg was administered by IM injection once monthly for 6 months. 160 male patients with prostate cancer were randomized. The primary endpoint was the proportion of successful patients over the total number of $ITT_{evaluable}$ population patients (i.e $N_{successes}/N_{evaluable\ patients}$). Success is defined as castration at day 28, no missing data at key time-points, i.e. days 28, 56, 84, 112, 140 and 168 and maintenance of castration through day 168. Castrate testosterone levels are defined as <0.5 ng/ml (= 50 ng/dl= 1.735 nmol/l).

The achievement of castrate levels of testosterone has been considered an acceptable surrogate endpoint for clinical efficacy in advanced prostate cancer clinical trials. Serum/Plasma testosterone concentrations indicative of chemical castration have generally been set at less than 50 ng/dl (0.5 ng/ml).

The preferred design to assess the efficacy and safety of this new leuprorelin formulation would have been a comparative study versus a marketed product which has been proven efficacious.
However, there is previous regulatory experience in which single arm studies with no comparator group and with testosterone castration levels as the primary efficacy endpoint have been finally considered sufficient for the demonstration of efficacy for GnRH analogs. Examples include Vantas (histrelin) and Eligard (leuprorelin). The reader is referred to CHMP opinion on Vantas following an article 29 referral EMEA/H/CHMP/247760/2007.
Overall, there are two approaches regarding the one-month dosing of leuprorelin products, 7.5 mg and 3.75 mg of leuprorelin acetate. Both of them provide castrate levels, even though the former would be maximum dose that is safe, whereas the latter would be the minimum dose that is effective.

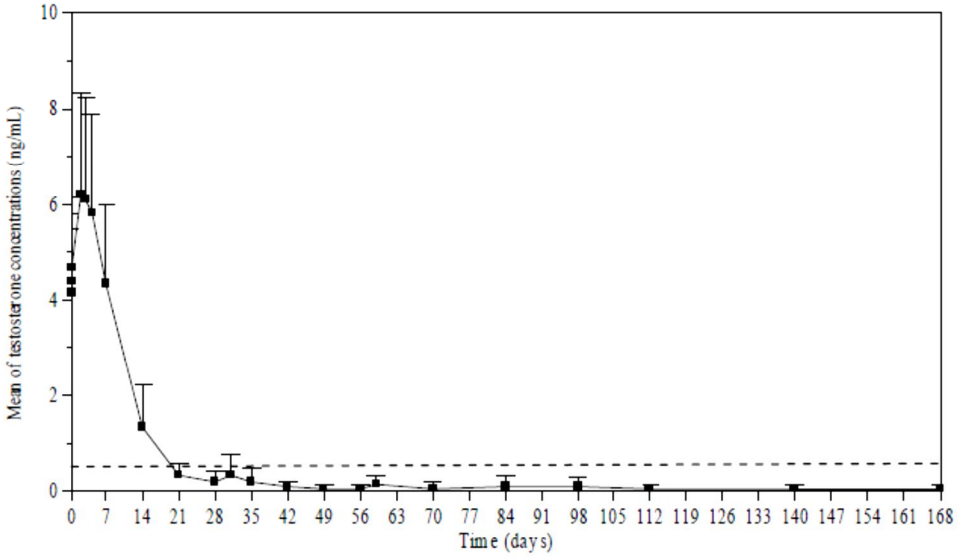
One hundred and sixty (160) patients were enrolled and all of them received at least one dose of the study medication. One hundred and fifty-four (154) patients completed the treatment and 152 (95% of enrolled patients) completed the study. $ITT_{evaluable}$ population consisted in 158 patients (98.75 % of the enrolled patients) and PP population consisted in 121 patients.

The mean age of the patients enrolled in the study was 71.6 years, ranging from 48-90 years.. In terms of race, 87.5 % of patients were Caucasian, 10 % were black and 1.9 % were Hispanic. Active medical history disorders reported were as expected considering age. Regarding

WHO/ECOG performance status at screening, 83.8% of patients had score 0 and 16.3% had score 2.

Histopathologic grade (G) at baseline was as follows: 9.4% of patients are classified as G1 (Gleason 2-4), 33.1% are G2 (Gleason 5-6) and 53.8% of patients are G3-4 (Gleason 7-10). From the 158 evaluable patients, 62 (40%) presented with advanced or locally advanced disease defined as T3 or T4 and/or N+ and/or M+ and 96 (60%) patients presented with early stages disease.

Figure 1: Mean (±SD) plasma testosterone concentrations (ng/mL) vs. time profile during treatment with 6 monthly i.m. administrations of 3.75 mg Leuprolide acetate GP-Pharm. A dashed line indicates testosterone castrate level (i.e. 0.5 ng/mL) throughout the profile Linear scale. Day 0 to day 168.



In the pivotal study for Lutrate Depot 3.75 mg, the proportion of patients that achieved castrate levels of testosterone at day 28 and maintained castration through day 168 was **96.20 %** (152/158), similar to the results that have been obtained in the pivotal trials with other leuprorelin formulations and with other GnRH agonists. However, the patients included in the study are not representative of the target population to be treated with GnRH agonists, i.e. patients with advanced prostate cancer; therefore the Company was requested to carry out an analysis for the efficacy primary endpoint on the advanced / locally advanced prostate cancer staging set of population.

A further analysis for the efficacy primary endpoint on the advanced / locally advanced prostate cancer staging set of population was performed. In this analysis we can observe that the percentage of patients with castration levels was 96.8%, whereas the outcome for the whole population of the study was 96.20 % (152/158). These results can be deemed similar to the results that were obtained from pivotal trials with other leuprorelin formulations and with other GnRH agonists.

Successful patients (Advanced prostate cancer staging set)	n (%)
Evaluable patients of advanced prostate cancer staging set	62
Number of successful patients in the advanced prostate cancer staging set	60 (96.8)
Exact two sided 95% confidence interval of the percentage of successful patients in the advanced prostate cancer staging set	(88.8 - 99.6)
p-value of exact two sided binomial test (alpha=0.05) in the advanced prostate cancer staging set	0.014488
Power (%) of exact two sided binomial test (alpha=0.05) in the advanced prostate cancer staging set	86.0

Importantly, even though the number of patients with advanced or locally advanced disease is relativity low (62 subjects; 40%) the result is pretty similar to the whole population of the study. This fact is pointing out an expectable finding. The use of a LHRH agonist gets its objective (testosterone levels < 0.50 ng/ml) independently of the stage of the disease. Therefore, there is no reason to believe that this product, Lutrate Depot, is going to show a different behaviour in terms of castration levels, depending on the patient's status disease. It is accepted that all leuprorelin products are highly effective.

Having said that, it is worth highlighting the importance of using this treatment in the actual target population (palliative treatment of advanced prostate cancer) given that, the primary pharmacodynamic effect of LHRH agonists is not directly related to the patients' disease. Of course, ultimately, the aim of this therapy is to provide palliative treatment in the advanced prostatic cancer setting and due to that, the wording of the indication must collect the actual population candidate of obtaining benefit from this therapy.

The Applicant agreed in rewriting the indication as "palliative treatment of locally advanced or metastatic prostate cancer".

Of note, others LHRH agonists already authorized as "palliative treatment of advanced prostate cancer" or similar, included patients in different stages of PC. In fact, in one open-label, multicenter, Phase 3 study, 138 patients with prostate cancer were treated with a single VANTAS implant (histrelin) and were evaluated for at least 60 weeks. Of these, 37 patients had Jewett stage C disease, 29 had stage D disease, and the remaining 72 patients had an elevated or rising serum PSA after definitive therapy for localized disease. Serum testosterone was suppressed to below the castrate level (≤ 50 ng/dL) in all 134 evaluable patients (100%) on Day 28.

Clinical safety

The Applicant has submitted 3 clinical studies as source of AEs; CRO-02-43, CRO-03-46 and CRO-04-62.

- CRO-02-43 was a Phase I trial in healthy male volunteers aimed to compare the testosterone suppressive effect of 2 Leuprolide Depot 7.5 mg GP Pharm formulations.
- CRO-03-46 was a Phase I trial in healthy male volunteers comparing the testosterone suppressive effect of Leuprolide Depot GP Pharm 3.75 and 7.5 mg vs. market references Lucrin® 3.75 mg depot Abbott and Procrin® 7.5 mg depot Abbott.
- CRO-04-62: Phase III trial in cancer prostate cancer. Pivotal study of this application.

In Study CRO- 04-62, no control arm was included. It was a single group study; hence, the absence of comparator could be considered a matter of concern in itself. Though on the other hand, in common with the clinical development of other leuprorelin products, it would not be considered necessary to undertake comparative studies between drugs because there is a valid, objective, established marker of castration, the achievement of castration levels of testosterone in serum to ≤ 50 ng/dl.

In fact, Eligard, (leuprorelin acetate) was authorised without comparative studies with other GnRH

analogues (DE/H/0508/01/MR). Additionally, the effects of leuprorelin over several years are well documented and do not differ substantially from those of other GnRH analogues given at appropriate dose levels, or from those after orchiectomy, on the accepted surrogate endpoint of testosterone suppression to ≤ 50ng/dl in serum. In summary, in assessor's view, no comparative studies are therefore considered necessary in patients.

The extent of exposure included 190 patients treated with leuprorelin, with 165 patients exposed to the medicinal product of this application. 160 were studied in the pivotal trial. Regarding the extent of exposure in the main study, one-hundred and fifty-four (154) of the 160 enrolled patients received 6 monthly doses of 3.75 mg Leuprolide acetate, GP-Pharm. Overall exposure for these patients was 22.75 mg Leuprolide. Six (6) subjects did not receive all 6 doses of investigational product.

Table 1: Study subject drug exposure by dose and duration of exposure

Study ID	Dose	Route	Number and type of subjects	Overall exposure
CRO-02-43	Formulation A: Leuprolide Depot GP-Pharm 7.5 mg	IM	5 healthy males	Single dose
	Formulation B: Leuprolide Depot GP-Pharm 7.5 mg	IM	5 healthy males	Single dose
CRO-03-46	T1: Leuprolide Depot GP-Pharm 3.75 mg	IM	5 healthy males	Single dose
	T2: Leuprolide Depot GP-Pharm 7.5 mg	IM	5 healthy males	Single dose
	R1: Lucrin Depot® 3.75 mg	IM	5 healthy males	Single dose
	R2: Procrin Depot® 7.5 mg	IM	5 healthy males	Single dose
CRO-04-62	Leuprolide acetate 3.75 mg	IM	160/160 prostate cancer patients	6 monthly doses=22.75 mg

IM: Intramuscular; R: reference formulation; T: test formulation.

Table 2: Exposure to Lutrate Depot 3.75 mg during study CRO- 04-62for the patients who received less than the 6 monthly doses

Center N. - Subj. N	Dose (mg)	Number of doses received	Total exposure (mg)
13-01	3.75	3	11.25
19-02	3.75	1	3.75
20-03	3.75	2	7.50
20-08	3.75	5	18.75
25-03	3.75	3	11.25
30-03	3.75	1	3.75

In the first two studies, CRO-02-43, CRO-03-46, no special AEs were reported substantially different from the described in the pivotal study. Most frequent AEs were headache, malaise and fatigue, hot flushes, libido decreased, and increased sweating. No differences were found, in terms of type of AEs, between the two formulations of leuprorelin depot GP Pharm and the comparators Procrin and Lucrin depot. No effects were observed on vital signs, electrocardiogram (ECG) or laboratory parameters. Nevertheless, due to the limited sample of the size of these studies, the value of the conclusions is not high enough.
The most common AEs observed in the pivotal trial were hot flushes (reported in 45% of total patients), fatigue (6.3%), asthenia (1.3%), hyperhidrosis (3.8%), night sweats (3.1%) and headache (3.1%). Cold sweat, erectile dysfunction, headache, breast swelling, breast tenderness, ejaculation failure, weakness and sleep disorders were experienced by the 0.6 – 1.3% of the patients.

A total of 35 local adverse reactions at the injection site were reported during the pivotal study. The most common local adverse reaction was injection site pain, which was experienced by 8.1% of total patients. Injection site irritation, discomfort, bruising, erythema were recorded for 4.4, 1.9, 1.3 and 1.3% of total patients respectively.

Table 3: Number of patients with most frequent related AEs by body system and preferred term

Category[a] Body system (SOC) Preferred term (PT)	Number of patients with related AE	Percentage of patients with related AE
Vascular disorder	**72**	**45.0**
Hot flush	72	45.0
Skin and subcutaneous tissue disorders	**14**	**8.8**
Hyperhidrosis	6	3.8
Night sweats	5	3.1
Cold sweat	2	1.3
General disorders	**13**	**8.1**
Fatigue	10	6.3
Asthenia	2	1.3
Nervous system disorders	**6**	**3.8**
Headache	5	3.1
Somnolence	1	0.6
Reproductive system and breast disorders	**4**	**2.5**
Erectile dysfunction	2	1.3
Metabolism and nutrition disorders	**4**	**2.5**
Increased appetite	2	1.3

[a] *Subjects may fall into more than 1 category.*

As it can be observed the most typical AEs were the hot flushes, which are related to the mechanism of action of leuprorelin.

Concerning the local AEs, intramuscular injections can result in skeletal muscle fibrosis, nerve injury or abscesses at the injection site. None of these AEs have been described in the studies submitted.

No clinically significant out of range nor clinically notable abnormal values for laboratory, vital signs or ECG parameters were observed throughout the study. No clinically relevant changes from baseline or shifts in values occurred during the entire study.

Regarding deaths, no deaths occurred during the studies CRO-03-46 and CRO-02-43. On the

other hand, in the pivotal trial, there was one death during the study. The death was due to disease progression and was not related to the study treatment.

No SAEs were reported in the first two studies.

In the pivotal study CRO-04-62 twenty-six SAEs were reported in 20 patients (12.5% of total patients) during the study. Of these, 2 SAEs were related to study treatment, were both experienced by one subject and consisted of pyrexia and back pain which required hospitalization. The patient was hospitalized. The two SAEs were not classified as "unexpected" because previously reported in the literature. The investigator reported that the symptoms were due to bone metastasis, already present at study entry, which worsened upon treatment. Concomitant medication was given to this patient as countermeasure.

Table 23. Number and percentage of SAEs classified by "body system" and "preferred term"

Category	Number of SAEs	Percentage of SAEs
SOC		
PT		
Any primary SOC	**26**	**100**
Cardiac disorders	**2**	**7.7**
Sick sinus syndrome	1	3.8
Sinus bradycardia	1	3.8
Gastrointestinal disorders	**1**	**3.8**
Gastritis	1	3.8
General disorders and administration site conditions	**3**	**11.5**
Disease progression	1	3.8
Pyrexia	2	7.7
Injury, poisoning and procedural complications	**1**	**3.8**
Meniscus lesion	1	3.8
Metabolism and nutrition disorders	**4**	**15.4**
Diabetes mellitus non-insulin-dependent	1	3.8
Hyperglycemia	1	3.8
Hypokalemia	1	3.8
Malnutrition	1	3.8
Musculoskeletal and connective tissue disorders	**1**	**3.8**
Back pain	1	3.8
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**1**	**3.8**
Lung neoplasm malignant	1	3.8
Nervous system disorders	**1**	**3.8**
Parkinsonism	1	3.8

Renal and urinary disorders	**5**	**19.2**
Hematuria	3	11.5
Urinary retention	1	3.8
Urinary tract obstruction	1	3.8
Skin and subcutaneous tissue disorders	**1**	**3.8**
Rash	1	3.8
Surgical and medical procedures	**5**	**19.2**
Anticoagulant therapy	1	3.8
Brachytherapy	2	7.7
Knee arthroplasty	1	3.8
Transurethral prostatectomy	1	3.8
Vascular disorders	**1**	**3.8**
Aortic aneurysm	1	3.8

PT: preferred term; SOC: System Organ Class.

No pharmacokinetic-based drug-drug interaction studies have been conducted with leuprorelin acetate.

The rate of withdrawals was low. Only two patients of the three studies carried out discontinued by AEs.

In conclusion, most of the treatment-related AEs are typically associated with testosterone suppression, such as hot flushes, fatigue or headache; or related to the injection itself, such as injection site pain. No treatment-related deaths occurred during the study.

III BENEFIT RISK ASSESSMENT

From a clinical point of view the use of leuprorelin in palliative treatment of patients with prostate cancer is widely known. There are several GnRH synthetic analogs already approved for this indication. The mechanism of action of these compounds produces a decrease in testosterone production, which, is generally reversible upon cessation of GnRH agonist therapy.

The pharmacodynamic response to Lutrate Depot 3.75 mg, reflected in plasma testosterone concentrations, is consistent with the PD response for other leuprorelin and other GnRH analogs formulations.

The selected dose for leuprorelin, 3.75 mg monthly, is marketed in several European countries.

Therefore, this application does not have important flaws in terms of dose selection or biological plausibility.

One pivotal study has been submitted. This was an open-label study, with no comparator group using the experimental drug during 6 months. The primary endpoint used is acknowledged as an acceptable surrogate variable (levels of testosterone ≤ 50 ng/dl). So, the results of the study highlight the expected effects of this GnRH synthetic analog. By day 28, 96.8% of the patients (151/156) had achieved castrate levels.

No special safety concerns have been raised during the clinical studies. Safety profile of leuprorelin includes AEs typically associated with testosterone suppression, such as hot flushes, fatigue or headache; or related to the injection itself, such as injection site pain. No treatment-related deaths occurred during the study.

The wording of the indication claimed by the Applicant has been modified to ***palliative treatment of locally advanced or metastatic prostate cancer***, which is the indication approved for the other GnRH analogues.

In conclusion the benefit risk ratio can be deemed as positive.

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