SCIENTIFIC DISCUSSION

Suprelorin 4.7 mg implant for dogs

1. SUMMARY OF THE DOSSIER

The active substance of Suprelorin 4.7 mg implant for dogs is deslorelin (as deslorelin acetate), a synthetic gonadotrophin-releasing hormone (GnRH) analogue. Deslorelin acts by suppressing the function of the pituitary-gonadal axis when applied in a low, continuous dose. This suppression results in the failure of treated animals to synthesise and/or release follicle stimulating hormone (FSH) and luteinising hormone (LH), the hormones responsible for the maintenance of fertility.

The product is well tolerated, however moderate swelling at the implant site may be observed for 14 days. Histologically, mild local reactions with chronic inflammation of the connective tissue and some capsule formation and collagen deposition have been seen at 3 months after administration. A significant decrease in testicle size will be seen during the treatment period. In very rare cases, a testicle may be able to ascend the inguinal ring. The approved indication is for the induction of temporary infertility in healthy, entire, sexually mature male dogs.

2. QUALITY ASSESSMENT

Suprelorin consists of a cylindrical shaped implant of 2.3 mm diameter and 12 mm length containing 4.7 mg of deslorelin (as deslorelin acetate). The implant is a solid, opaque, white to pale yellow cylinder weighing 50 mg in total, which is intended for subcutaneous administration to dogs.

Composition

Suprelorin contains 5.85 mg/implant of deslorelin acetate 85.5% as active substance. The excipients are hydrogenated palm oil, lecithin and sodium acetate anhydrous.

Container

The primary packaging is a pre-loaded implanter. Each implanter is in a sealed foil pouch, which is sterilised as a whole unit. The secondary packaging is cardboard cartons containing 2 or 5 individual sterile foil-sealed implanters and 1 implanting device (actuator) per carton.

Clinical Trial Formula

Several batches have been used in clinical evaluations with a range of active content per implant (5-8 mg), active concentrations and sodium acetate levels. All batches were manufactured by the finished product manufacturer outside of the EEA, and several batches were made using the final formulation proposed for marketing.

Development Pharmaceutics

The development objective for Suprelorin was to formulate a sustained release, subcutaneous implant for use in dogs. The finished product is formulated to contain 5.0 mg deslorelin per implant (the label claim is 4.7 mg deslorelin per implant). An active substance overage compensates for loss during the manufacturing and sterilisation process.

The excipients have been chosen to adjust the release rate of the water-soluble deslorelin acetate from a lipophilic matrix and also to ensure that the matrix is fully biocompatible. The ingredients are mixed into the product, which then is formed into rods via extrusion. The lipophilic matrix and the mechanism for the active substance release were considered to be adequately described.

The implant length and diameter of 2.3 mm gives the product a suitable mechanical strength.
The implants are terminally sterilised.

After sterilisation there was a decrease in the active substance and a consequential increase of related substances occur. During manufacture an active substance loss occurs. The total loss of active substance is compensated for by an adequate active substance overage. Individual levels of deslorelin and known and unknown impurities were provided for 9 batches pre and post irradiation.

The primary packaging is an implanter system consisting of a separate pre-loaded implanter and a common actuator system, which minimises the material to be sterilised. A sterilised spacer in the implanter ensures that the non-sterile actuator does not contaminate the implant. The implanter is sealed in laminate foil, sterilised as a whole unit and then placed in a cardboard carton as secondary packaging, which also holds the common actuator.

An HPLC method has been developed for deslorelin assay and content uniformity. A separate HPLC method has been developed for related substances. Both methods have been validated and were considered to be acceptable.

A dissolution test methodology has been developed, according to the Ph.Eur. The choice of dissolution method has been justified.

Method of Manufacture

The manufacturing formula for the commercial batch size was presented. A flow chart of the manufacturing process was presented and found to be acceptable. The manufacture involves 4 stages, which were described in detail in the dossier.

The implants are produced by an extrusion process. Initially, the active ingredient is densified and mixed with the lyophilised excipients to form a dry powder blend. This blend is then mixed with the remaining excipient and screened to produce an homogeneous blend. This blend is tabletted to form slugs that are subsequently milled to produce a free flowing granulate which can be fed into the extruder. The extruded material is cut to produce uniform implants of the correct weight and size. The implants are loaded into the implanters, which are individually sealed in laminate foil pouches and sterilised.

Appropriate in-process controls are carried out during the process.

A validation protocol of the manufacturing process and results from the first validation batch were presented. The validation of the sterilisation process was found to be acceptable.

Control of Starting Materials

Active Substance

The active substance is not described in a pharmacopoeia so an in-house monograph was developed.

The in-house specification for the active substance was considered satisfactory and included tests for description, identification, specific optical rotation, pH of solution, purity, related substances, acetate content, water content, mass balance, peptide content, bioburden, bacterial endotoxins and residual solvents. The related impurities acceptance criteria lists named/known individual impurities, “each individual unknown” and “total” impurities; justified acceptance criteria were presented.

Applicants' Parts of the two European Drug Master Files (EDMFs) were included in the dossier. Details of the identity, manufacturing site, synthesis and control of the active substance were provided. Evidence of structure data were provided from a variety of techniques, and the physico-chemical properties were described. Impurities and residual solvents were described, and limits applied in the specification were justified.

Validation reports for the following analytical procedures, carried out by the finished product manufacturer, were presented: acetate by HPLC, purity by HPLC and related substances by HPLC. A detailed comparison of the finished product manufacturer's HPLC methods and the active substance manufacturers' methods was also presented.

Certificates of Analysis (CoAs) have been generated by the finished product manufacturer on deslorelin acetate. All the results comply with the proposed in-house specification. The finished product manufacturer carries out the following testing on the active substance: appearance, identification, pH, purity by HPLC, related substances by HPLC, acetate content by HPLC and water content. For the remaining tests, the finished product manufacturer accepts the active substance manufacturer's CoA results.

Excipients

All of the excipients are of pharmacopoeial grade. Where there is no European Pharmacopoeia monograph available, another pharmacopoeial monograph (either the British Pharmacopoeia or United States Pharmacopoeia, where applicable) has been adopted and justified. In-house specifications and testing methodologies for the excipients have been provided, which demonstrate compliance with the relevant pharmacopoeial monographs.

Packaging

Specifications were included for the packaging materials and CoAs were provided.

Special Measures Concerning the Prevention of Animal Spongiform Encephalopathies

No materials of animal origin are used.

Control tests on Intermediate Products

Specifications have been established for the 2 key intermediate products. The key intermediate specifications include parts of the active substance specification and the finished product specification and were found to be acceptable.

Control Tests on the Finished Product

Tests for identification and quantitation of the active substance include identity, assay, content uniformity and dissolution. Deslorelin related substances determination is carried out. The test for sterility is according to the relevant Ph.Eur. monograph.

The analytical methods have been adequately validated in accordance with EU and VICH Notes for Guidance and are described in detail in the dossier. A report detailing the method development of specifications and dissolution profiles was provided. The sterility test method validation report was presented.

Batch data and the CoAs for 5 batches were presented which demonstrate that the specification is consistently met.

Stability Tests on the Active Substance

Stability data for the active substance were submitted. These results support the storage condition "Store in a freezer (less than -18°C) which has been defined in accordance with the guideline EMEA/CVMP/99-Rev.2-FINAL "Note for Guidance on Declaration of Storage Conditions: B) For Active Substances". Based on the stability data for deslorelin acetate, which shows that at 25°C over 3 months, the maximum increase of an impurity peak is 0.2%, there is no need to transport the deslorelin acetate under frozen conditions.

Stability Tests on the Finished Product

The finished product end of shelf life specification was provided. The proposed specifications are the same as proposed for release, except the assay limits which were widened and the related substances limits which were increased slightly.

Stability studies for 24 months indicate that no changes occur in the physical parameters during storage. Dissolution and appearance are not affected and it seems unlikely that these two parameters would be unaffected if changes in the physical quality of the implants appeared during storage. Photostability tests were not considered relevant as this particular product is presented in foil packs and there is no light exposure during administration.

These results support a shelf-life of 2 years when stored at 2-8°C. The proposed storage conditions "Store in a refrigerator" and "Do not freeze" are also acceptable.

Other Information

A declaration that VICH Topic GL18 (Residual Solvents) is complied with was provided.

Overall Conclusion on Quality

Satisfactory data have been provided with regard to the active substance and the finished product. Control tests of the finished product cover the relevant quality criteria and are suitable to confirm adequate and consistent product quality.

The product contains no starting materials as defined in section 2 of the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy via Medicinal Products.

The data support a shelf life of 2 years.

Overall the data provided in Part II was considered satisfactory and was shown to be compliant with current guidelines.

3. SAFETY ASSESSMENT

Pharmacology

Gonadotrophin releasing hormone (GnRH) stimulates the secretion of FSH and LH from the pituitary gland. This release of FSH and LH is responsible for the subsequent production of gonadal hormones. FSH/LH release is further regulated by feedback mechanisms of the gonadal hormones. Normally, GnRH is released in a pulsatile manner, which also gives a pulsatile release of FSH/LH. However, continuous administration of GnRH leads to desensitization and down-regulation of GnRH receptors on pituary gonadotrophs, thereby inhibiting gonadotrophin and gonadal hormone release.

In the male, LH stimulates the Leydig cells to produce androgens (mainly testosterone), whereas FSH acts on Sertoli cells to control spermatogenesis. Continuous administration of GnRH agonists therefore acts indirectly on testosterone secretion from the testes by inhibiting secretion.

Toxicological studies

No toxicological data were available for deslorelin as no studies have been conducted in laboratory animals. The toxicity findings for the synthetic peptide deslorelin are expected to be related to its pharmacological action. For all toxicological endpoints, the applicant refers to data for buserelin, another GnRH analogue with similar affinity for rat pituitary GnRH receptors.

Deslorelin differs from buserelin by a single amino acid residue (D-tryptophan versus a tertiary butylated D-serine). The incorporation of this residue serves to increase the receptor affinity but is not critical for receptor activation itself. Due to the very similar peptide sequence and pharmacological properties, the results from the buserelin safety studies may be considered as representative for deslorelin.

Single dose toxicity

Although this endpoint was not investigated for deslorelin, acute toxicity would probably result in increased levels of LH and FSH. Suppression of fertility would not be expected, as this is the result of chronic exposure of GnRH.

Repeated dose toxicity

A 26-week repeated oral toxicity study was presented with doses of buserelin up to 200 µg/kg/day in rats and dogs. In rats, a dose related decrease in testicular weight was observed. In dogs, this decrease was not dose related and was seen at all treatment levels together with inhibition of spermatogenesis, prostate atrophy and increase of Leydig and interstitial cell numbers. Testosterone secretion and synthesis was reduced, but progesterone production was not significantly affected.

A table detailing the adverse events seen in clinical studies with deslorelin was presented. The dogs in two of these studies were treated for up to 2.5 years and good clinical tolerance was reported.

Toxicity after repeated dosing is not expected. In the clinical studies, only data in relation to efficacy were collected together with target animal safety data, which consisted of physical examination at the time of implantation. Taking into account data on carcinogenicity studies with buserelin and, particularly, data on target animal tolerance studies and observations in humans, the limitations of the repeated dose toxicity data were considered acceptable.

Reproductive toxicity, including teratogenicity

No data were presented for deslorelin; all available data were for buserelin.

Groups of pregnant mice received buserelin acetate via subcutaneous injection at doses of 0.01, 1, 100 and 10000 µg/kg/day on days 6-15 of gestation. All dams in the 0.01 µg/kg/day group were allowed to litter normally and nurse their pups until lactation day 21. Approximately two thirds of dams from the 1 and 100 µg/kg/day dose groups underwent caesarean section on gestation day 18, while the remainder were allowed to deliver spontaneously. All 10000 µg/kg/day dams underwent caesarean section.

The only treatment-related effect seen at necropsy was an increase in ovarian weight and the number of corpora lutea (1 µg/kg/day and above). Duration of gestation and the birth index was reduced (1 and 100 µg/kg/day). Viability index at LD4 and the weaning index were favourable at all dose levels. There were no abnormalities in the external appearance, bones, internal organs, postnatal growth or development, including reproductive development of F1 pups or F2 foetuses and neonates. It was concluded that the NOEL was 0.01 µg/kg/day.

Embryotoxicity/foetotoxicity, including teratogenicity

Groups of pregnant mice were administered buserelin acetate via subcutaneous injection at doses of 0.1, 1, 10, 100 and 1000 µg/kg/day, from gestation day 15 to lactation day 21. Prolonged parturition and an increased number of stillborn pups were observed at doses of 1 µg/kg/day and above. However, offspring from treated females reportedly showed no compound-related changes in any of the parameters examined, including morphological, functional, and behavioural development and fertility. The authors concluded that the NOEL was 0.1 µ g/kg/day.

Buserelin was administered subcutaneously to pregnant rabbits at doses of 0.1, 1 and 10 µg/kg/day during the first and second trimester, day 6 to 18 of gestation. Reduced birth index, reduced number of corpora lutea and number of live foetuses and an increase in the weight of internal organs were seen from 1 µg/kg/day. A NOEL of 0.1 µg/kg/day was established.

All data available are for buserelin. Buserelin was shown to reduce gestation length, but prolong parturition and decrease the number of live offspring in treated mice. A decrease in the number of live foetuses was also seen in treated rabbits. However, buserelin showed no signs of teratogenic potential, and the development and fertility of live offspring appeared unaffected. An overall NOEL of 0.01 µg/kg/day was established.

In view of the structural and pharmacological similarity of buserelin and deslorelin, and the likely pharmacological basis for any adverse reproductive effects, the presentation of data for buserelin was considered appropriate. Additionally, it is acceptable to use buserelin data to justify embryotoxicity for deslorelin as it is not intended for use in female animals.

Mutagenicity

Genotoxicity studies are not deemed necessary, therefore no data for deslorelin were submitted.

Carcinogenicity

As no data for deslorelin are available, a carcinogenic study in rats performed with buserelin was submitted.
Due to the peptide nature of such GnRH analogues, these compounds would not be expected to possess any mutagenic potential. Consequently, carcinogenic potential, were it to exist, would be expected to be mediated by a non-genotoxic, pharmacological mechanism. As such, the presentation of data for buserelin within this application was considered justified.

Groups of male and female rats were administered buserelin acetate at doses of 0, 0.2, 0.6 and 1.8 µg/kg/day for 24 months. Testicular weight was reduced in males at the top dose, and histopathology revealed testicular tubular atrophy with hyperplasia of the Leydig cells. Leydig cell hyperplasia is an expected pharmacological response to the lack of LH stimulation. Although buserelin has been marketed for several years, there are no reports that buserelin treatment increases the incidence of Leydig cell

tumours. The benign Leydig cell tumours observed in the rat carcinogenicity study occurred in a non-dose related manner with similar incidence in the control and the highest-dose groups. No malignant tumours were observed in the study. In summary, the risk for the target animal species for developing malignant Leydig cell tumours following deslorelin treatment is considered neglible.

Studies of other effects

No immunotoxicological data for deslorelin are available. Data for buserelin were submitted and no antibody formation against buserelin was observed in long-term studies in rats, dogs, monkeys and humans. It is unlikely that antigenicity would occur with GnRH such as deslorelin due to the low molecular weight and close structural relationship to natural GnRH.

Observations in humans

The applicant has submitted seven references for observations seen in humans after potential use of deslorelin. Use of deslorelin has been investigated for children (boys and girls) with precocious puberty and women with premature ovarian failure. Use of deslorelin for treatment of symptoms associated with prostate cancer in men has also been investigated. The submitted data from the use of deslorelin in humans confirm the expected lack of toxicity. A search for more recent data on the safety of deslorelin in humans was carried out to ensure that no new knowledge of risks has emerged for the active substance.

Microbiological studies (studies on human gut flora and organisms used in food processing)

These studies are not considered relevant, as the product is not intended for food-producing animals.

Studies on metabolites, impurities, other substances and formulation

The peptide is expected to undergo hepatic metabolism, in the same manner as natural peptides, with amino acids excreted in the urine. Therefore, deslorelin metabolites are not likely to pose a risk for the user. This is further supported by the lack of adverse reactions in the pharmacovigilance reports from Australia after the use of 1200 individual doses of Suprelorin. The excipients are derivates of lecithin and palm oil that are natural excipients and are widely used in medicinal preparations. Lecithin is characterised as a Generally Regarded As Safe (GRAS) compound.

User Safety

A satisfactory user safety risk assessment (conducted in accordance with CVMP guideline 'Guideline on User Safety for Pharmaceutical Veterinary Medicinal Products' (EMEA/CVMP/543/03)) was presented.

Inherent Toxicity

In reprotoxicity studies with buserelin, the NOEL was established as 0.01 µg/kg/day, with adverse effects relating to the reproductive system starting from 1 µg/kg/day. No irritation studies are available for deslorelin, but studies performed with buserelin in dogs and rabbits did not evoke any adverse effects after intranasal, conjunctival, intravenous, intramuscular or subcutaneous administration.

Exposure of the user

An overview of the possible hazards connected to the use of Suprelorin was presented. Since the product is a preloaded implanting device intended for use by professional users only and together with the fact that veterinarians are experienced in the use of other implants for use in dogs (e.g. for ID marking), it is considered relatively safe for users to handle the product.

Conclusion including the risk management proposals

The four potential hazards that are listed by the applicant are included in the SPC:

Pregnant women should not administer the product. Another GnRH analogue has been shown to be foetotoxic in laboratory animals. Specific studies to evaluate the effect of deslorelin when administered during pregnancy have not been conducted.

Although skin contact with the product is unlikely, should this occur, wash the exposed area immediately, as GnRH analogues may be absorbed through the skin.

When administering the product, take care to avoid accidental self-injection by ensuring that animals are suitably restrained and the application needle is shielded until the moment of implantation.

In case of accidental self-injection, seek medical advice immediately, with a view to having the implant removed. Show the package leaflet or the label to the physician

Ecotoxicity

The applicant has only provided a phase I assessment as a phase II assessment is not considered necessary because the product will only be used in non food-producing animals. Furthermore, the used implant is not removed before a new implant is inserted, therefore, handling and disposal of used implants will not be necessary.

Conclusions on Safety

The safety file was based on the similar properties for deslorelin compared to buserelin, as all submitted toxicological data concern buserelin, except for observations in humans and the target animal safety study (see Efficacy). Similar to other GnRH analogues, deslorelin is not expected to pose significant toxicological risk following exposure, instead, any potential risks would be related to its pharmacological activity. It is therefore considered that data for other GnRH analogues may be used to document lack of risk.

Following acute exposure to GnRH analogues an initial increase in LH and FSH secretion is expected. A dose dependent decrease in reproductive organ weight and testosterone concentration is observed following repeated or chronic exposure, which reflects the documented pharmacological mode of action of GnRH analogues.

In conclusion, the toxicological file was considered sufficient and acceptable for this type of substance for veterinary use.

4. EFFICACY ASSESSMENT

Pharmacodynamics

Gonadotrophin releasing hormone (GnRH) stimulates the secretion of FSH and LH from the pituitary gland. This release of FSH and LH is responsible for the subsequent production of gonadal hormones. FSH/LH release is further regulated by feedback mechanisms of the gonadal hormones. Normally, GnRH is released in a pulsatile manner, which also gives a pulsative release of FSH/LH. However, continuous administration of GnRH leads to desensitization and down-regulation of GnRH receptors on pituary gonadotrophs, thereby inhibiting gonadotrophin and gonadal hormone release.

In the male, LH acts to stimulate the Leydig cells to produce androgens (mainly testosterone), whereas FSH acts on Sertoli cells to control spermatogenesis. In females, FSH promotes ovarian growth, follicular maturation and subsequent secretion of oestradiol, whereas LH is essential for ovulation and development and release of progesterone by the corpora lutea. GnRH agonists, therefore, indirectly inhibit testosterone secretion from the testes by inhibiting secretion of LH and FSH. Testosterone is essential for complete functioning of the seminiferous tubules and maintains the morphology and function of the prostate in dogs. It is also required for optimal libido.

The different GnRH analogues contain substitutions at position 6 which protects against proteolysis and substitutions at the C-terminus that improves receptor-binding affinity. Compared to natural GnRH, deslorelin has a D-Trp amino acid instead of Gly at position 6, and N-EtNH_2 in the C-terminus instead of Gly-NH_2. The relative potency of deslorelin is stated to be approximately 150 times that of natural GnRH.

Demonstration of therapeutic effects

Three references studying the chronic effects of deslorelin in male dogs were presented. The references detail the effect of deslorelin on histological findings in the male reproductive system after between 40 and 100 days of deslorelin administration: the seminiferous tubules show exfoliation of the germ cells into the lumen and become atrophic and aspermatogenic. Spermatozoa disappear from the lumen of the ductus epididymis. Sertoli and Leydig cells show marked atrophy. Severe atrophy of the prostate nucleus is seen and the epithelium becomes non-secretory.

These findings were also observed after administration of other GnRH agonists.

A further reference also describes the reversible effects in dogs after treatment with deslorelin. The dogs were treated with 50 µg/kg sc. daily for 4 months and were allowed recovery of additionally 4 months whereafter the testes were examined histologically. After 4 months, a complete return to normal spermatogenesis and Leydig cell morphology was observed. Clinical effects include: reduced testicular size, reduced ejaculate volume, reduced sperm count and reduced libido.

A review of data relating to nafarelin and deslorelin (GnRH agonist) treatment and return to fertility of the male animals was provided. The data show a restoration of reproductive function (testosterone and ejaculation returned to normal), and histological appearance and spermatozoa were detected in the lumens of normal epididymal ducts. The prostate tissue also returned to normal. The evidence indicates that the clinical effects of the treatment are reversible. A paragraph regarding the number of animals returning to normal plasma testosterone levels within 12 months (80%) and within 18 months (98%) of implantation, in the studies conducted by the applicant, was added to the SPC. The SPC also includes the wording "however, data demonstrating the complete reversibility of clinical effects (reduced testicular size, reduced ejaculation volume, reduced sperm count and reduced libido) including fertility, after six months, or repeated implantation, are limited."

Reference levels for normal plasma testosterone concentrations are 2 – 4 ng/ml. Chronic GnRH administration is shown to inhibit testosterone release. Therefore, the applicant has presented a scientific

justification to support the use of plasma testosterone levels as a surrogate marker for infertility. Infertility is defined as the inability to impregnate a bitch.

The use of plasma testosterone levels as a surrogate marker for infertility is necessary because more direct measures of fertility, such as semen collection, are not possible during periods of suppressed testosterone levels. Several references describe the effects that have been noted in dogs with decreased plasma testosterone levels in response to treatment with GnRH agonists: decrease of ejaculate volume to nearly zero for nafarelin and deslorelin with testosterone levels from 2 ng/ml to 0 ng/ml; inability of spermatozoa to penetrate oocysts after leuprolide treatment with testosterone levels decreased from 13 ng/ml to 0 ng/ml; sperm counts drop to nearly zero parallel to decreased testosterone levels from 3 ng/ml to 0.02 ng/ml after deslorelin treatment; reduced sperm motility by 70%; reduced penis enlargement and erection and absence of thrusting or ejaculation; decrease in testicular volume with testosterone levels dropping from 3 ng/ml to below 1 ng/ml.

It is stated that a testosterone level of <0.4 ng/ml in male dogs will correspond to functional infertility. The threshold of 0.4 ng/ml was chosen based on an Expert review of the above mentioned references and the studies with deslorelin performed by the applicant (i.e. clinical trials, PhD thesis) where testosterone levels below 0.4 ng/ml almost entirely ruled out semen collection by digital manipulation.

The dogs included all showed suppression of testosterone levels within 9-20 days after initial treatment. There was then a lag phase until complete suppression of fertility was achieved, within 23-33 days, as indicated by plasma testosterone levels of <0.4 ng/ml. The conclusion on the available data is, therefore, that within 6 weeks after treatment, dogs will be functionally infertile. In summary, Suprelorin brings about a reduction in plasma testosterone levels and this has been shown to closely correlate with an inability to impregnate a bitch.

The SPC includes a warning to "Keep all treated animals away from bitches on heat, for six weeks following the first implantation, if impregnation of that bitch, by the treated dog, is to be prevented."

Secondary pharmacodynamic effects

No data are available on the secondary pharmacodynamic properties of deslorelin. However, secondary effects have been investigated for other GnRH agonists. For leuprolide, minor effects were observed in *in vitro* and *in vivo* studies in guinea pigs, mice, rats, rabbits and cats. 10 mg/kg s.c. to rats produced sedation and decreased locomotor action. At concentrations from 3-10 mg/kg s.c. to anaesthetised cats, leuprolide did not have any effect on the respiratory and cardio-vascular system. Suppressive effects on male and female accessory sex organs and on the placenta have also been described for GnRH. It is suggested that GnRH or GnRH-like peptides may play a role in the CNS acting as a neurotransmitter since exogenous administration of GnRH modulated sexual behaviour in experimental animals.

Drug interactions

A paper documenting that efficacy of a GnRH agonist is not affected by an antiandrogen was submitted. Furthermore pharmacovigilance data together with the studies performed by the applicant did not reveal any signs of drug interactions. An overview of concurrent administrations of drugs during the trials was presented. A total of 21 administrations are listed, where deslorelin has been administered concurrently with different antimicrobials, NSAIDs and antiparasitics. Information was provided by the veterinary investigators during the trials. No reports of interaction have been reported from Australia, where the product is marketed.

Pharmacokinetics

Data were presented describing the pharmacokinetics of deslorelin and the GnRH analogue buserelin. GnRH analogues such as buserelin are expected to exhibit very similar pharmacokinetics to deslorelin due to structural similarity and similar relative resistance to degradation.

There are a number of practical difficulties involved in assaying deslorelin and other GnRH analogues in blood. These include the expected low concentration in blood and rapid degradation following entry into the systemic circulation. Although more stable than GnRH itself, GnRH analogues are rapidly absorbed and rapidly eliminated, predominantly by hepatic metabolism to peptide fragments and individual amino acid residues, following parenteral administration. The mean elimination half-life of the analogue buserelin has been reported to be approximately 72-80 minutes, regardless of the route of administration. A plasma clearance value of 34.3±5.48 ml/min/kg has been reported for deslorelin in rats following intravenous administration of a single 100 µg/kg dose.

Excretion is primarily via the urine. In female, human, endometriosis patients treated with buserelin, the mean percentage of the dose recovered in urine as immunoreactive buserelin within 24 hours of administration was 16.7%, 12.6% and 0.17% after intravenous, subcutaneous and intranasal administration, respectively.

Efforts were made to develop a suitable method for the assay of deslorelin levels in dog plasma. A radioimmunoassay (RIA) technique developed was unable to assay deslorelin at plasma levels below 40 pg/ml. However, data generated from trials using this technique provide insight into the early stages of absorption and distribution of deslorelin, up to approximately 2.5 months after administration of a radio-labelled deslorelin implant.

A study of plasma concentrations of deslorelin in 10 implanted dogs after the use of two different test batches containing 5 mg deslorelin (5 dogs per batch) was presented. There were considerable differences in the ADME profile of ^{125}I-deslorelin from the two batches for the first 40 days post implantation (PI). The differences in plasma profiles are a reflection of the inability to accurately assay plasma for deslorelin with the radioimmunoassay (RIA) technique that was developed. Despite the very different plasma levels between the two batches, it is concluded that deslorelin levels peak within 7-35 days PI. Plasma deslorelin levels drop down to the limit of quantification (40pg/ml) by around D50-70 PI

Recovery of deslorelin from Suprelorin implants administered to mice was presented. The four batches used were identical to the ones used in the clinical trials performed in Australia. Male mice aged 8-12 weeks were administered the implant. Control mice were used to compare weight and adverse reactions. At preestablished time points, the mice were weighed and euthanased and the implant was recovered in order to measure the remaining amount of deslorelin. On average, 31.4% of deslorelin was released within the first 4 weeks. A mean rate of release was 52.7 µg/day. This level decreased over the next 22-26 weeks with mean concentrations of 14.9 µg/day. No weight loss or adverse reactions were observed between control or implanted mice. A weight gain was seen in the implanted mice, but it should be noted that the relative dose administered to these mice (~5 mg per 50 mg BW) was approximately 400,000 times that administered to dogs (~5 mg per 20 kg BW) and, therefore, these data cannot be used to assess the physiological effects of deslorelin in animals.

Release from the implant can be considered similar between species. The release rate of the active ingredient is most likely due to the physico-chemical properties of the implant rather than the environment the implant is put in. This is also confirmed by the *in vitro* studies performed. As long as the implant site is in a vascularised area, the difference in species should not be relevant. The release rate as seen in the mice study can therefore be compared to release rates in dogs.

Tolerance in the target species of animal

Target animal safety study

One GLP Target Animal Safety study performed in 1998 was submitted. In this study a batch was used, which contains slightly different contents of deslorelin and acetate. A table in the expert report gives an overview of content:

Product details:	Tolerance Study	Pivotal Studies
Batch No(s):	1 Batch	3 Batches
Implant description: Active/total (mg)	6mg/67mg	5mg/50mg
% deslorelin	9	10
% acetate	3	1.5
Excipients	Admul, Epikuron	Admul, Epikuron

Dogs used were equal numbers of Beagles age 13-19 months. Deslorelin was administered in doses of 12x recommended dose, i.e. 10 implants of the composition detailed above were administered at the same time in each of the dogs. Clinical observations were made daily the first 14 days and weekly thereafter. Observations included changes in general health and the reproductive system, body weight, food consumption, body temperature and clinical chemistry. Furthermore, local tolerance was studied at every implant site (10 per dog) D14, D28, D56 and D84 after implantation. Scores were given for swelling, soreness, hardness, inflammation, necrosis and persistence at implant site. From D0-14, studies of local tolerance were included in the daily general clinical observations. The dogs were necropsied at D91 and target observations in the male dog included plasma levels of testosterone and LH, effects on pituitary, hypothalamus, testes, epididymis and prostate.

All dogs remained in good health throughout the study. Physical examination did not reveal any effect on body temperature or behaviour. Some soft faeces were observed in the animals, but this was not persistent and is considered unrelated to treatment. Body weight was measured every month and of the female dogs one had a small decrease in bodyweight (11.0 D0 – 9.9 D91), but this could be related to the decrease in food consumption, that was observed for the females, but not for the males.

Clinical chemistry showed normal parameters within the reference ranges for adult beagles, however, a clear decrease in alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase were observed in the female dogs, which were not considered to be of any clinical significance. The only haematology parameter that showed any significant change was activated partial thromboplastin time that in all animals went from 6.8-8.3 seconds to 12.2-13.9 seconds.

An expert statement was submitted that comments on the increase in activated partial thromboplastin time (aPTT) values seen in the TAS study. The expert concludes that the increase is most likely not related to physiological relevant changes but is more a matter of technical skills and sampling methods within the laboratory. Moreover, the aPTT values are within reference intervals for normal dogs from two different laboratories (Cornell University and Schering Corp).

Furthermore, if clinically significant increases in aPTT were presenting in dogs in this study, clinical signs consistent with defective secondary haemostasis would be present (haemorrhage into joints and body cavities; joint swelling; shifting lameness; haemothorax; haemoperitoneum; haemarthrosis). Signs of external haemorrhage such as epistaxis, haematemesis, melaena and haematuria may be seen. None of these clinical signs were reported in any of the dogs in this study and no changes associated with secondary haemostasis were found at gross post mortem examination or on histopathology. In addition, no clinically significant signs associated with defective secondary haemostasis have been recorded in dogs treated with Suprelorin, in any of the preclinical or clinical studies.

Testosterone levels were also measured, but only until D28, where a decrease was observed in the male dogs. Progesterone levels increased in the female dogs. LH levels decreased in all dogs to 0.26-0.57 ng/ml. All of these changes are expected effects of a GnRH analogue, when administered to male or female dogs.

In the reproductive system, decrease in organ weights, as expected after treatment of a GnRH analogue, was observed. One female showed hyperplasia of the glandular epithelium of the mammary gland. Moderate swelling at some implant sites were observed in the first 56 days in half of the dogs, however,

this swelling was only related to soreness at D14 in some of the implant sites. Hardness was observed in many of the implant sites throughout the observation period. No inflammation or necrosis was observed macroscopically. Persistence at implant site demonstrated by palpation was evident throughout the observation period, meaning that the implant did not migrate from site of administration. At necropsy, examination of the implant sites revealed chronic inflammation of the connective tissue with minimal to mild capsule formation and collagen deposition. One animal had moderate infection in three implant sites on D3, which was treated with penicillin, without sequelae.

It is stated that there was no observed gynaecomastia in either of the male dogs in the tolerance study or any other male dogs in their clinical studies. Looking at the primary effects of implantation with deslorelin, which reduces FSH and LH, it is expected that steroid hormones in the treated males would be reduced in level. A review of the literature involving humans treated with GnRH agonists for prostate cancer showed that none of the references found refer to the effect on gynaecomastia in patients receiving GnRH agonists alone. Gynaecomastia has not been reported in men or animals receiving GnRH agonists.

Tolerance data from clinical studies

The applicant has presented safety data from the clinical trials. Of the dogs treated with Suprelorin adverse reactions 2.4 % of adverse reactions due to treatment with Suprelorin were reported. These included a report of bleeding at the implant site and in one of the repeated administration studies, a dog was diagnosed with a temporarily absent/shrunken left testicle.

Of the dogs treated some 24% dogs received repeated treatments, 4 times in one study and at present 5 times in another study (an interim report was submitted for this ongoing study). Beside the absent testes as mentioned above, one dog in a study died from a focal, necrotizing myelopathy due to embolism of invertebral disk material. The clinical signs described and the post mortem findings were not attributed to Suprelorin treatment and are consistent with a diagnosis of fibrocartilaginous embolism (FCE). No other adverse reactions were reported after repeated use of Suprelorin.

Physical examinations were carried out prior to treatment with Suprelorin and during the observation periods in all of the clinical trials, at the time points detailed. However, investigators only recorded unusual clinical observations, which were reported as adverse events. This is confirmed in a statement signed by the investigators.

Pharmacovigilance data

The applicant has also presented pharmacovigilance post marketing data from Australia. One report classified as Suspected Lack of Expected Efficacy was received. A Japanese Spitz weighing 6 kg, and reported to be less than 12 months of age was implanted with Suprelorin and 3½ weeks later the female pup in the house showed her first signs of heat. One week later, the owner discovered the two dogs trying to mate and one month later the bitch was diagnosed pregnant. The applicant concluded that the product was not used according to label, as it is stated in the SPC that male dogs should be kept away from bitches in heat for at least 6 weeks after the first implantation.

The efficacy of Suprelorin in pre-pubertal dogs has not been investigated. Therefore, the following, additional wording has been included in the SPC under section 4.5 (Special precautions for use in animals):

“The use of Suprelorin in pre-pubertal dogs has not been investigated. It is therefore recommended that dogs should be allowed to reach puberty before treatment with Suprelorin is initiated.”

Clinical Studies

Laboratory trials

Dose-determination studies

The applicant has presented a number of studies which were designed to determine the optimal dose of deslorelin required to suppress plasma testosterone levels to below 1 ng/ml (a threshold set by the study director) in sexually mature, entire male dogs for a period of six months. In all these studies dogs were implanted with the same peptide deslorelin as in the final formulation Suprelorin. In all studies dogs were administered the implant subcutaneously. Differences between the batches used in these studies and Suprelorin were in the composition of the lipid and pore-forming matrix. However, they essentially consisted of the same lipids, in similar proportions and slight changes in the pore former content of the matrix. As these were dose determination studies, and the dose has subsequently been confirmed in dose confirmation studies conducted with Suprelorin, the expert considered this approach to dose selection to be both justifiable and acceptable.

A study used dogs between 5-38 kg bodyweight that were assigned into four groups: 0, 3, 6, or 12 mg of deslorelin. Blood samples were taken in order to measure testosterone levels in all dogs. Testosterone levels were presented for all dogs and measurements were available for up to 2170 days for controls, up to 554 days for the 3 mg group, 1116 days for the 6 mg group and 1451 days for the 12 mg group. 40% dogs in the 6 mg group died for reasons wholly unrelated to the administration of Suprelorin. In the 12 mg group, 60% of dogs were re-implanted, because this was a pilot study and it was decided to investigate the effect of re-implantation of animals.

In all dogs, testosterone levels were suppressed after implantation. Testosterone levels were below the threshold of 1 ng/ml at the latest at D23. No significant difference was observed in the time taken for testosterone levels to initially drop. Testosterone levels in 40% of the dogs in the 3 mg group returned to above 1 ng/ml before six months from the date of implantation. From graphs that were presented by the applicant, it can be seen in the 3 mg group that testosterone levels still fluctuate and that the dose is not sufficient to suppress testosterone levels constantly. In contrast, for the dogs that received 6 or 12 mg implants, all except one maintained suppressed (< 1 ng/ml) plasma testosterone levels for at least 309 days. In the 6 mg group, in one dog (which was euthanased due to a diagnosis of immune mediated haemolytic anaemia) an increase in testosterone level was observed in the last measurement, D198. In the 12 mg group, dogs did not start to increase in T-levels before D800. Based on this study, the applicant concluded that at dose of more than 3 mg and less than 6 mg would be sufficient to suppress testosterone levels to <1 ng/ml for approximately 6 months.

Dose- confirmation studies

In another study dogs initially received 4 mg deslorelin and were then re-implanted on D316 with 6 mg deslorelin following recovery to normal testosterone levels.

Testosterone levels were suppressed to <1 ng/ml in the dogs at D7-43 after first implantation. At D162 the first dog started to increase in testosterone levels and at reimplantation day (D316) all dogs had testosterone levels above 1 ng/ml. The dogs were then re-implanted with a 6 mg implant. From D35 after re-implantation, all dogs had testosterone levels below the threshold. Testosterone levels started to increase again in one dog at D308 after the 6 mg (second) implant, followed by the other dogs at D378-589.

The results from this study using 4 and 6 mg implants in dogs, i.e. a dose-response relationship with regard to duration of testosterone suppression, must be viewed in light of the limited data collection. The overall conclusions of the study, i.e. that a dose between 4 and 6 mg will suppress the testosterone production for approximately 6 months, is considered sufficiently valid.

The applicant has presented a PhD thesis on veterinary reproduction where two trials provide supportive evidence in regards to dose-determination**.** The thesis was partly funded by the applicant.

Trial 1 was a placebo-controlled study using male dogs implanted with 6 mg deslorelin; in one group male dogs were implanted with a placebo implant and in another, male dogs served as untreated control dogs. The treated dogs were re-implanted with an identical implant after they had shown full recovery of spermiogenesis after the first implant (approx. 1 year later). All dogs were between 2 and 3 years of age. Definition of suppressed testicular function was testosterone levels below 0.65 ng/ml, that no ejaculate could be obtained, and a significantly reduction in testicular size. Parameters investigated were: testicular size, bodyweight, testosterone and LH levels, semen collection and characteristics, and histology of testes, epididymis and prostate at the end of the study.

Results:
Plasma testosterone levels and LH levels was suppressed from D21 – D 280.
Testicular size decreased in all dogs treated. Size dropped significantly from D35 and maintained decreased levels until D294-392 after implantation. One dog had a significant smaller size left testes after recovery compared to before treatment.
Semen was collected weekly for 5 weeks before treatment, 5 weeks after implantation, 5 weeks prior to recovery and 5 weeks after recovery. Semen could not be collected from week 6 to week 48. Recovery was the day when ejaculates were collected successfully.

During the first 5-6 weeks the semen characters changed markedly, as can be seen from the table above. After 6 weeks PI no ejaculates could be collected and it was not possible to collect ejaculates again before 48 weeks PI (336 days PI).

No significant changes in body weight gain were noted over the 470 days the dogs were observed (1.68±0.46 kg for controls and 2.85±0.9 kg for treated). After recovery, all eight stages of spermiogenesis were present in the seminiferous tubules. Leydig cells had normal appearance. Spermatozoa were observed in epididymis. It is concluded that the inhibitory effect of treatment with 6 mg deslorelin over 6 months are fully reversible in the dogs due to increase in LH and testosterone levels and recovery of testicular function.

The study supports that treatment results in suppression of testosterone levels and reduced fertility from 5 to 48 weeks after treatment. Full recovery of semen characteristics was seen approximately 1 year after treatment with 6 mg deslorelin. The inter-individual variation is noted and is reflected in the SPC. No statistically significant difference was detected in volume, motility, concentration and abnormalities at 5 weeks before implantation and 5 weeks after successful collection of semen. The nature of abnormalities is not described in details.

Trial 2 used dogs weighing 15-32 kg and between 2-4 years of age. The male dogs were divided into three groups, implanted with 3 mg, 6 mg and 12 mg, respectively. The control dogs from trial 1 were reused in this study. The same parameters as in trial 1 were investigated, i.e. testicular size, bodyweight, testosterone and LH levels, semen collection and characteristics, and histology of testes, epididymis and prostate at the end of the study.

Results were comparable to the above described study, where the same doses of deslorelin were used. In the 3 mg group, number of days of suppression was 231-672. In the 6 mg group, the number of days of suppression was 371 to more than 553. In the 12 mg group, the number of days of suppression was more than 504-672 for all dogs, since no sign of recovery was evident at the end of the study. In addition, the results indicate that the lowest concentration (3 mg) had a faster onset of efficacy, that is to say, suppression was seen at early time than for the 6 mg and 12 group. However, there is no statistical or biological reason to believe that this was a “real” effect. It is concluded from this study that the dose-response relationship of the groups was not on the degree of the effect, but on the duration of suppression.

The applicant has presented a statistical meta-analysis of the plasma testosterone level data obtained in field trials using the final formulation of 4.7 mg. The purpose of this analysis was to profile changes in testosterone levels over time.

Of the treated dogs in the study (of which 3.6% died during the course of the study, for reasons unrelated to the administration of Suprelorin), at time of analysis, 80% dogs had records for at least 180 days. A total of almost 98% maintained testosterone levels below 1 ng/ml until 180 days (6 months) post implantation. However, the time to control (that is, testosterone under the 1 ng/ml level) for 95% of the treatment dogs was 30 days (1 month) post implantation, with 5% of dogs taking in excess of this. The one dog that failed to be controlled for the 180 day period maintained a level under 1 ng/ml up to day 154, but its level increased to be 3.44 ng/ml on day 168 and 2.48 ng/ml on day 183.

The dose-determination studies performed by the applicant show a dose-response relationship in regards to the duration of suppression of testosterone and normal fertility. The higher the dose used; the longer the average duration of suppression. The optimal dose seems to be between 4 and 6 mg. The inter-individual variation is very large and is reflected in the SPC.

As supplemental data, the applicant has submitted a PhD thesis, where dose-determination studies have been performed, using 6 mg in one trial and 3, 6 and 12 mg in another trial. Semen characteristics were examined before and after treatment. In all of the dogs treated, successful collection of ejaculates by digital manipulation was not possible until almost a year after implantation. Semen analysis was performed and indicated that recovery of spermatogenesis was possible after one implantation of deslorelin. The abnormalities in spermatozoa that were found after recovery were not described in detail, but the frequency of abnormalities was equal to pre-treatment levels. Some dogs treated with 6 and 12 mg did not return to fertility within the time of the study, i.e. > 1.5 years.

The choice of 4.7 mg as the dose in the final formulation was sufficiently demonstrated.

Field trials

Five clinical studies were presented. In three studies Suprelorin was given as a single implant and in two studies implantation was repeated (4 and 5 times, respectively). All studies were GCP with the same design, except for the repeated treatments.

A general description of the study design is given below:

<table>
<tr><td colspan="2">Mature gonad-intact male dogs, divided into three groups: <10 kg, 10-25kg, >25kg
A control group of dogs was used throughout all clinical studies.
The dogs were housed at the research site during the study.</td></tr>
<tr><td colspan="2">Treatment: Suprelorin implant 4.7 mg (single or repeated) at T0,</td></tr>
<tr><td>Pretreatment investigations (T-5):
Testosterone levels
Testicular size
Semen analysis</td><td>Clinical parameters:
Plasma testosterone levels (D0, 2 x weekly in the first 3 weeks, 1 x 14 days from week 4-52)
Testicular size (weekly the first 3 weeks, 1 x 14 days from week 4-52).</td></tr>
</table>

Other observations:
General health (times not specified)
Implant site adverse reactions (daily first two weeks, at blood sampling times)
Semen analysis and sexual behaviour (times not specified)
Duration of sexual dysfunction:
Time to return to normal reproductive potential using all or any of the criteria:
Scrotal circumference or testicular measurement
Plasma testosterone levels

Semen analysis and sexual behaviour

The precise age of the dogs is not given for all dogs, but all were adult. Breed and weight before and after treatment is given in most dogs. As the dogs were purchased by the University, the dogs have been housed under kennel-like conditions. The slight average weight gain observed could have several reasons, since no specific control of this is mentioned (change in food, exercise etc) and it is within acceptable ranges.

Results

Single implant, dogs almost equally divided in the three groups

Pre-treatment parameters:

The applicant presented a summary of semen-analysis for the dogs included and it was concluded that parameters for all dogs are considered normal to justify inclusion in the study.

Testosterone levels:

In the expert report, a summary of plasma testosterone level suppression was presented. Suppression = < 1ng/ml testosterone. However, reanalysis was performed in response to questions asked by the CVMP, with suppression defined as plasma testosterone levels <0.4 ng/ml. The results given below take into account this re-analysis.

Group	1 (<10 kg)	2 (10- 25 kg)	3 (>25 kg)
Deslorelin dose (mg/kg)	0.51- 1.31	0.22- 0.31	0.11- 0.18
First day of suppression	7- 36	9- 28	14- 43
Last day of suppression	196- 561	140- 505	183- 364
Mean duration of suppression (days)	404	263	244

It was concluded that rapid lowering of plasma testosterone levels were seen in all dogs with levels <0.4 ng/ml within 6 weeks. This suppression was maintained for at least 24 weeks in all but 8.8% of dogs, which showed increased levels after 18 - 23 weeks. Mean period of suppression were reduced as bodyweight increased.

Testicular size:
The mean testicular size was reduced in all dogs from an overall mean of 13.1 cm, which equals placebo dogs, to 10.1 cm after 63 days. A mean reduction of 20-30% was maintained for 43 weeks (315 days). Testicular size was returned to almost pre-treatment sizes less than two years after implantation.

Semen analysis:
The applicant presented a summary of mean semen data from D0-35 after implantation. The results only include data from some dogs in group 1 and 3.

It was stated that libido was absent from D35 and onwards. The applicant has submitted raw data on semen collection. It can be seen that many of the successful semen collections included ejaculates with semen abnormalities. No description of the abnormalities, in terms of characteristics or severity, was provided.

Mean days until successful collection for group 1 was 507 days and that did not include 2 dogs that were never reported to have successful collection. For group 2, mean days were 478 and this only included data for 40% of dogs, as the remainder were not reported to be successful or were not collected. For group 3, mean days were 425 that did not include 39% of dogs as they were not reported to be successful or were not collected. For all three groups, the mean days for successful collection were longer than mean days of suppression of testosterone levels.

Adverse reactions:
No adverse reactions in relation to implantation were reported. In the raw data, all adverse reactions were listed. None of them were possibly related to administration of Suprelorin. One dog was euthanised due to a diagnosed parvovirus infection.

Conclusion:
It is concluded that this study demonstrates the safety and efficacy of Suprelorin in inducing infertility in entire males from 6 weeks PI to approximately 6 months PI.

Single implant, dogs of 10-25 kg)

Pre-treatment parameters:

91% were collected before treatment. Average sperm motility was 79.5% (45-90) with 10.7 % (2.5-45.5) tail abnormality and 1.25% (0-2.5) head abnormality. No data were available on sperm concentration and viability. One dog received placebo treatment.

Testosterone levels:
In the expert report, a summary of plasma testosterone level suppression is presented, which has been modified to reflect a plasma testosterone level threshold of <0.4 ng/ml, indicating suppression:

Weight range (kg):	14.6- 20.8
Deslorelin dose rate (mg/kg):	0.23- 0.35
First day of suppression:	8- 50*
Last day of suppression:	175- 386
Mean duration of suppression (days):	261

*D50 for one dog only; all others were suppressed by D36

The mean period of suppression was 9-10 months and all dogs returned to plasma testosterone levels above 0.4 ng/ml after 1.5 years.

Testicular size:
Testicular size decreased until D25 with about 10% and decreased further from D79 to D218 with a reduction between 20.6-25.2% of initial size. Testicular size did not return to pre-treatment sizes for up to 12 months. In one dog testicular size returned after 17 months.

Semen analysis:
The applicant presented a summary on semen analysis. From the raw data, it can be seen that many of the successful collections of semen late in the study showed abnormalities in the semen and had to be repeated. One dog still had unsuccessful semen collection at D604. Mean day until successful collection of semen was 261, which was the same as the mean duration of suppression measured by plasma testosterone levels (261 days).

Adverse reactions:
No adverse reactions were reported. The reported reactions were listed, mostly skin and ear disorders, but these were not related to the use of Suprelorin.

Conclusion:

It was concluded that the study demonstrated the efficacy of Suprelorin in inducing infertility from 6 weeks up to 25 weeks after a single implantation.

Single implant, dogs of 10-25 kg

Pre-treatment parameters:
42% of dogs were selected for semen analysis throughout the study. At D0 average volume of semen was 1.7 ml with a head abnormality of 0.4% and a tail abnormality of 10.1%. No other semen characteristics were reported. 1 dog was placebo treated with an empty implant.

Testosterone levels:
In the dossier a summary of plasma testosterone suppression is presented, which has been modified to reflect a plasma testosterone level threshold of <0.4 ng/ml, indicating suppression:

Weight range (kg):	13.2- 28.0
Deslorelin dose (mg/kg):	0.22- 0.36
First day of suppression:	7- 22
Last day of suppression:	183- 296
Mean duration of suppression (days):	232

All dogs were suppressed until more than six months PI and all returned to plasma testosterone levels of higher than 0.4 ng/ml after less than one year PI.

Testicular size:
At D43, mean testicular size was 84.3% of the initial size and a decrease of 20-30% was maintained for 140 - 210 days. Thereafter, an increase in mean size was observed, up to 94% of the original size by 44 weeks PI.

Semen analysis:
The applicant has presented a summary of the 42% of dogs that had semen collected:

Adverse reactions:

No serious adverse reactions were reported in relation to treatment. One dog had transient bleeding and swelling at the implantation site, which is not considered unexpected.

One dog (PW328) mated and tied with its run mate at D330, which was 55 days before successful collection was obtained, but with a testosterone level D331 of 2.45 ng/ml. It is not unusual that a dog may mate following recovery of normal plasma testosterone levels (330 days after implantation), but before semen could be collected by digital manipulation.

Conclusion:
It is concluded that this study demonstrated the efficacy of a single implant of Suprelorin in inducing temporary infertility from 22 days PI until at least 26 weeks PI.

4 repeated implants, dogs in different groups

Pre-treatment parameters:
This study used mainly dogs from the single implant with dogs in different groups study that had recovered from suppressed testosterone levels and all had plasma testosterone levels >1 ng/ml before first implantation. One dog was newly enrolled and had not participated in that study but in another trial where it had received 7.5 mg deslorelin and had plasma testosterone levels of 0.98 ng/ml before implantation. There are no data available for any dogs on semen analysis before treatment.

Dogs were implanted four times at six monthly intervals.

Testosterone levels:
The expert has not provided an overview on suppression on testosterone levels, but based on raw data, the following conclusions could be drawn:

Testicular size:
By D28 dogs began to show decreased testicular size. All, but one dog had at D70 more than a 15 % reduction in size, this reduction increased to up to 30% in some dogs from D70-720. One dog did not show signs of returning to normal pre-treatment size within the study period.

Semen analysis:
There are no data available on semen analysis from the beginning or the end of the study. Only data available are days of successful collection. Mean days for successful collection of semen was 1041 days for the one dog in group 1, 862 days for group 2 and 917 days for group 3. One dog in group 2 was never successfully collected. Time period before successful collection were considerably longer (up to 6 months after restoration of normal plasma testosterone levels) for all groups compared to suppression of testosterone.

Adverse reactions:

One dog mated a bitch when it had testosterone levels below the threshold at D476, which was in a period during treatment with the 3rd implantation. However, the mating did not result in pregnancy, confirming that the dog was infertile, as indicated by the plasma testosterone levels. This mating behaviour may have been a learned response, but a learned behaviour such as this does not indicate that the dog was fertile.

Another dog's run mate whelped and was fertilized in a period when the treated dog was not successfully collected, but after cessation of the suppressive effects of the forth and final implant. This dog mated the bitch 330 days after the male was given the implant, six weeks following the commencement of recovery. The dog was well into recovery at the time of the mating and testosterone was first noticed to be increasing at day 288. The mating was followed up and the bitch was subsequently diagnosed as pregnant, indicating reversal of infertility of the dog.

The SPC contains wording which accurately reflects the expected outcome of matings observed either during or after the period of expected plasma testosterone level suppression.

Conclusion:
The applicant concludes from this study that suppression of gonadal function (based on plasma testosterone levels) started after 13 - 43 days PI and lasted until at least 162 days after the last implant was administered. Results from testicular size and semen collection supported the primary efficacy parameter.

4 repeated implants, dogs of 10-25 kg

Pre-treatment parameters:
The dogs received five implants at 6 month intervals, however, the expert notes that the fifth implant failed quality assurance tests and therefore excluded the data.

Testosterone levels:
Suppression of testosterone levels below the threshold starts by D36 (60% of dogs) until D49 after implantation. Six months later the next implant was administered and at that day, 30% of dogs had testosterone levels >0.4 ng/ml. This decreased rapidly, by day 23 after the second implantation. From the second implantation onwards, all testosterone levels were below 0.4 ng/ml for the whole period, in all but one dog.

Testicular size:
From D36 and onwards, the dogs developed a 15% reduction in testicular size that lasted the whole period investigated, even in those dogs where a transient increase in plasma testosterone levels was observed. Only one dog was longer in developing a 15% reduction, but this was obtained by the time the second implant was administered.

Adverse reactions:
No treatment related adverse reactions were observed in the study period.

Conclusion:
The applicant concludes that most dogs had testosterone levels below the threshold within 36 days and maintained these levels following all subsequent implants. Three dogs had higher testosterone levels around D180, but as collection of semen was unsuccessful and since testicular function is not restored until 8 weeks after normal plasma testosterone levels return, all dogs, without exception, remained functional infertile.

CONCLUSIONS

The applicant has provided data from 5 clinical studies under field conditions using the final formulation of Suprelorin. The majority of dogs were in the weight range of 10-25 kg. Only few dogs under 10 kg or over 25 kg were used.

The results from the clinical studies and the discussions put forward are primarily based on testosterone levels, as the applicant uses a testosterone threshold (<0.4 ng/ml) as demonstration of efficacy. Measurement of testosterone levels supplemented with testicular size and unsuccessful semen collection are sufficient parameters to support suppression of testicular function, which has been demonstrated with the results from the clinical studies. The applicant has proved reduction of testosterone levels, reduction of testicular size, decreased libido and spermatogenesis from no more than 6 weeks after treatment and lasting for approximately 6 months in most dogs. The reversion to full fertility has, however, not been fully documented. The majority of dogs will regain normal semen characteristics approximately one year after last treatment, but for some dogs in the studies the reversion to normal fertility was not observed by the end of the study period.

Studies showed a dose-dependent duration of effect, which was reflected in the field studies as longer duration of effect in the smaller dogs. This was analysed and details are included in the SPC.

V. Risk Benefit Assessment

The active substance deslorelin acetate is a synthetic nonapeptide analog of LHRH (luteinizing hormone-releasing hormone), where the 6th amino acid in the native molecule is substituted with D-tryptophan.

The excipients are considered acceptable, as well as the packaging material, which is an implant device (implanter system) consisting of a separate pre-loaded implanter and a common actuator wrapped in foil laminate pouches and sterilised as a whole unit.

The finished product is an implant, which is intended for subcutaneous administration to male dogs for making them temporarily infertile. The rationale for choice of formulation is acceptable. Major issues regarding release of active substances from the implants (dissolution), validation of the non-standard manufacturing processes and related substances have been resolved.

A shelf-life of 2 years has been applied and is supported by stability data. Overall the quality data are considered acceptable (commitments have been made by the applicant to provide further data).

The safety file is based on the similar properties for deslorelin compared to buserelin, as all submitted toxicological data concern buserelin, except for observations in humans and the target animal safety study.

Similarly to other GnRH analogues, deslorelin is not expected to pose significant toxicological risk following acute exposure. Instead, any potential risks would be related to its pharmacological activity. Since the dossier contains observations in humans and safety data in target animals for deslorelin, and deslorelin exhibits the expected pharmacological effects for a GnRH analogue, it is agreed that data for other GnRH analogues may also be used to document lack of risk due to the close relation in pharmacological activity and that no further toxicological studies with deslorelin are required. Following acute exposure to GnRH analogues an initial increase in LH and FSH secretion is seen. A dose dependent decrease in reproductive organ weight and testosterone concentration is observed following repeated or chronic exposure, which reflects the documented pharmacological mode of action of GnRH analogues. The diffuse Leydig cell hyperplasia, observed in carcinogenicity studies with buserelin, as a risk to dogs, was investigated and found to be not relevant for the product.

The toxicological file is considered overall sufficient, as generally accepted for this type of substance for veterinary use. The applicant has searched for more recent data on the safety of deslorelin in humans, where it has been used for a number of years, which has demonstrated that no new knowledge of risks has emerged for the active substance.

The Applicant has provided published references and studies in the target animal to support the demonstration of the pharmacodynamic effects of GnRH agonists, including deslorelin, on the male reproductive system. Clear evidence is provided that chronic administration of deslorelin will reduce the functionality of the male reproductive organs and the plasma testosterone levels. The scientific justification for using plasma testosterone as surrogate marker for reduced fertility by Rhodes et al. is acceptable. However, normal plasma testosterone levels are highly variable and fluctuate considerably, with numerous peaks during a 24 hour period. It is acknowledged that continuous low levels of testosterone correlates with reduced fertility, and the chosen threshold was fixed after analyses of the data in the dossier.

The reversibility of the changes on the Leydig and prostate cells and on the last phases on spermatogenesis (spermiogenesis) was addressed after 4 months treatment in dogs with deslorelin. This supports the reversible effect on spermatogenesis after treatment with deslorelin in male dogs, although Suprelorin is intended for at least 6 months of treatment and repeated treatments for prolonged periods are foreseen.

Fertility will not instantly return to normal once testosterone levels are restored to normal as spermatogenesis in the dog takes about 8 weeks. It would, therefore, not be expected that dogs that have been suppressed will have normal spermatogenesis for at least 8 weeks after plasma testosterone levels return to normal. The return to normal spermatogenesis has, however, not been fully investigated. Since a very low risk for permanently reduced fertility was identified in one of the studies, a warning for future breeders has been included in the SPC.

No apparent interactions with other drugs were identified in any of the studies and in available pharmacovigilance data, but the data are limited and a comment has been included in the SPC.

The applicant has provided information on the pharmacokinetics of GnRH agonists by published references and studies. A study in dogs with a radio-labelled formulation showed that deslorelin concentrations in plasma varied between batches and between animals. A release study in mice using four batches of Suprelorin in the final formulation showed the recovery of deslorelin in implants removed at different time intervals after implantation. These batches were also used in the clinical studies and recovery was less variable between batches. Pharmacokinetic studies performed with the final formulation in the target species are not presented in the dossier.

It is recognised that GnRH levels can be difficult to measure for numerous reasons, and also elimination is fast. Moreover, it is the pharmacological action of GnRH analogues, which does not necessarily correlate with plasma levels that are of importance. Therefore, precise pharmacokinetic data for deslorelin are not considered pivotal information in this application.

However, the dog study gives an indication on high inter-individual variability and the applicant has commented on the relation between variability in release from the implant and the variability of the duration of suppression of testosterone that was observed in the clinical studies.

A well performed target animal safety study has been submitted. Dogs were administered 10 implants at the same time. The study showed good general tolerance and mainly the expected pharmacological effects on the reproductive system. The study also showed good local tolerance of Suprelorin with only mild reactions, which are described in the SPC. The applicant also presented the clinical repeat-dose studies for documentation of tolerance of long-term treatment. The clinical studies are focused on the long-term effects on the reproductive system, primarily limited to testosterone levels and testicular size and possibility of collecting semen from dogs by digital manipulation. In the study protocol for the clinical studies, general tolerance by physical examination was investigated but no data are available except reports on adverse reactions.

Effects in pre-puberty dogs have not been demonstrated. The onset of puberty is often related to large variations in GnRH hormone peaks. It seems reasonable that male dogs should be allowed to go through puberty before a supression treatment like Suprelorin is started. The indication has been limited to comprise healthy, entire, sexually mature, male dogs.

The dose-determination studies performed by the applicant show a dose-response relationship in regards to the duration of suppression of testosterone levels and normal fertility. The higher dose used, the longer the average duration of suppression. The optimal dose seems to be between 4 and 6 mg. The inter-individual variation has been analysed and is reflected in the SPC.

The applicant has focused the choice of optimal dose on plasma testosterone levels primarily. In the dossier, some reports are from early in the product development and lack important information on the study design and characteristics of the dogs. As supplemental data, the applicant has submitted a PhD thesis, where dose-determination studies have been performed, using 6 mg in one trial and 3, 6 and 12 mg in another trial. Semen characteristics were examined before and after treatment. In all of the dogs treated, successful collection of ejaculates by digital manipulation was not possible until almost a year after implantation. Semen analysis was performed and indicated that recovery of spermatogenesis was possible after one implantation of deslorelin. The abnormalities in spermatozoa that were found after recovery

were not described in detail, but the frequency of abnormalities was equal to pre-treatment levels. Some dogs treated with 6 and 12 mg did not return to fertility within the time of the study, i.e. > 1.5 years.

The choice of 4.7 mg as the dose in the final formulation is considered sufficiently demonstrated. The goal of the applicant was to find a dose that suppressed testosterone levels sufficiently for at least 6 months, and from the clinical studies this seems to be a near optimal dose. There is, however, variability between individuals in regards to suppression that seem to be related to body weight. Information regarding the variability has been included in the SPC.

The applicant has provided data from 5 clinical studies under field conditions using the final formulation of Suprelorin. The majority of dogs were in the weight range of 10-25 kg. Only few dogs under 10 kg or over 25 kg were used, especially in the repeat-dose studies.

The results from the clinical studies and the discussion by the applicant and expert are primarily based on testosterone levels, as the applicant uses a threshold testosterone level as a surrogate marker of infertility, for the demonstration of efficacy.

Measurement of testosterone levels supplemented with testicular size and unsuccessful semen collection are considered sufficient parameters to support suppression of testicular function, which has been demonstrated with the results from the clinical studies.

The applicant has proved reduction of testosterone levels, reduction of testicular size, decreased libido and spermatogenesis from no more than 6 weeks after implantation. The temporary infertility induced by Suprelorin cannot be expected to last for more than 6 months but, equally, reversion to full fertility has, however, not been fully documented. The majority of dogs will regain normal semen characteristics approximately one year after last treatment, but some dogs in the studies did not. A special warning has been included for intended future breeder dogs. Studies showed a dose-dependent duration of effect, which was reflected in the field studies as longer duration of effect in the smaller dogs. This was analysed and included in the SPC. The applicant has addressed the expected outcome in cases where a treated dog mates and ties with a bitch in heat. This information is also included in the SPC.

Directions for the removal of an implant, if the owner wishes to end the treatment are also included in the SPC. Studies of other effects, e.g. behavioural changes have not been performed and words to this effect are included in the SPC.

Based on the original and complementary data presented, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the quality, safety and efficacy of Suprelorin were considered to be in accordance with the requirements of Council Directive 2001/82/EC, as amended.

Suprelorin 9.4 mg implant for dogs

I Summary of the dossier

An application for an extension of a Community marketing authorisation of Suprelorin was submitted to the Agency on 28 July 2009 by Virbac S.A. in accordance with Article 2(a) of Commission Regulation (EC) No 1085/2003 and Annex II thereof. Suprelorin contains deslorelin and is presented in packs of 2 and 5 implants preloaded in implanters and with an actuator. It is indicated for the induction of temporary infertility in healthy, entire, sexually mature male dogs for up to 6 months and this extension application concerns a doubled strength (9.4 mg) and prolonged duration for up to 12 months. The route of administration is subcutaneous use. The target species is dogs.

The pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

No inspection issues have been identified during the assessment of the application.

A valid GMP certificate for finished product manufacturer has been issued in March 2007 GMP certification is also enclosed for the batch releasers (Brecon and Virbac) and the two active substance manufacturers (ASM).

II QUALITY

II.1 Composition

The formulation is an implant containing 9.4 mg deslorelin acetate (9.4%) in a matrix consisting of hydrogenated palm oil (HPO) and lecithin. Ethanol anhydrous is used as granulating agent but disappears during manufacture.

II.2 Container

The primary packaging is a pre-loaded implanter. Each implant is pre-inserted into a stainless steel needle casing of an implanter, which is then sealed with a needle cap and Luer lock. Each pre-loaded implanter is wrapped in a sealed foil pouch. The secondary packaging comprises cartons containing either two or five implanters, with a package insert and one implanting device (actuator) and package leaflet per carton. The packaging material is identical to that approved for the already authorised 4.7 mg strength.

II.3 Development Pharmaceutics

The development work is based on previous work performed for the approved 4.7 mg strength. Satisfactory descriptions of this work are provided in the dossier. Compared with the approved strength the excipient sodium acetate anhydrous has been omitted, with the intention to slow the release even more.

Improvements on the manufacturing process have been made, although the process is basically the same as that approved for the 4.7 mg strength. The same overage is also applied. Dissolution profiles of batches used for clinical trials tend to be faster than production batches for commercial use. However, it has been shown by f2 values that the dissolution profiles of the commercial batches are comparable to the average of the clinical batches.

II.4 Method of manufacture

The manufacturing process consists of an initial freeze drying of deslorelin acetate to produce the intermediate densified deslorelin acetate which is mixed with a blend of freeze dried HPO and lecithin. The mixture is compressed into slugs, dry granulated and screened. The product is formed into a rod via a low temperature extrusion process and the implants are cut to the desired weight by a rotary cutter. The implants are loaded into the implanters, which are individually sealed in laminate foil pouches. These are packaged in cardboard cartons. The cartons containing the foil wrapped pre-loaded implanters are sterilised using the same conditions as approved for the 4.7 mg strength. Validation has been performed on several batches. However, as the manufacturing process is considered a non-standard process, further validation data are requested as a follow-up measure before the proposed batch size can be accepted.

II.5 Control of starting materials

Active substance

The active substance is sourced from two active substance manufacturers (ASM). Documentation from both ASM has been provided as an EDMF. No changes have been made compared to what was approved during the procedure for the 4.7 mg strength.
Retest periods approved are:

- 24 months when stored in a high density polyethylene opaque powder bottle fitted with polypropylene screw cap at -15°C (freezer) or 2-8°C (refrigerator) for the first ASM.
- 12 months when stored in a Type III amber glass bottle fitted with polypropylene screw cap with a Teflon insert at -18°C for the other ASM.

Excipients

The excipients comply with relevant pharmacopoeias.

II.6 Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

No materials are of animal origin.

II.7 Control tests during production

Appropriate specifications have been established for the two key intermediate products; densified deslorelin acetate and packed implant prior to irradiation. Holding times are as proposed and accepted for the 4.7 mg strength.

II.8 Control tests on the finished product

Appropriate specifications identical to those agreed upon during the procedure for the 4.7 mg strength have been proposed and accepted. The analytical methods used are mainly isocratic and gradient HPLC methods. Dissolution is checked in accordance with Ph. Eur. Batch analyses confirm the proposed limits.

II.9 Stability

Stability studies have been performed on pilot and production scale batches. Batches have been manufactured with active substance from each of the proposed sources at 5°C and 25°C/60% RH for up to 24 months. Decrease in assay and increase in related substances are observed during stability. The stability data justify a shelf-life of 2 years with the storage conditions "*Store in a refrigerator (2°C to 8°C), Do not freeze*". As a follow-up measure it is a precondition that data from the ongoing stability

studies performed on the production scale batches will be provided to EMA when 2 years' data are available.

II.10 Overall conclusions on quality

The extension application for the higher strength of Suprelorin 9.4 mg is acceptable with only a few issues to be resolved as follow-up measures, namely the applicant commits to presenting further validation data for at least two commercial batches of the proposed 5000 implant batch size when available and to presenting the data from the on-going stability studies on the remaining production scale batch when the 2 years' data are available. The dossier submitted contains the missing information requested during the approval procedure for the 4.7 mg strength and thereby it complies with relevant requirements for this type of product.

III Safety

This is an extension application for Suprelorin 9.4 mg implant for the induction of temporary infertility in healthy, intact male dogs for a minimum duration of 12 months. Most data included in Part III of the dossier were also submitted and assessed for Suprelorin 4.7 mg.

III.1.1 Pharmacodynamics

Refer to Efficacy section.

III.1.2 Pharmacokinetics

No new *in vivo* ADME data were generated for Suprelorin 9.4 mg. Compared with Suprelorin 4.7 mg the applicant has excluded sodium acetate from the 9.4 mg formulation to reduce the release rate of deslorelin. Therefore, *in vitro* dissolution data have been presented to illustrate the differences in release rates for the two formulations. While the dose of Suprelorin 9.4 mg is twice as high as that of Suprelorin 4.7mg, less than twice the quantity of deslorelin is released from Suprelorin 9.4 mg each day. The use of an *in vitro* study to mimic the *in vivo* situation was well supported by the applicant.

III.1.3 Toxicological studies

Single and repeat dose toxicity

No new data were presented. Toxicity after acute or repeat dosing is not expected, except for the pharmacological effects on the reproductive organs. Only toxicological data for buserelin, another GnRH analogue, were presented for Suprelorin 4.7 mg. Due to the very similar chemical structure and the pharmacological properties, the results were considered representative for deslorelin.

Tolerance in the target species of animal

Refer to Efficacy section.

Reproductive toxicity

No new data were presented. All data presented for Suprelorin 4.7 mg consisted of buserelin data. This was accepted.

Mutagenicity / genotoxicity

No data were presented. According to the CVMP MRL Summary Report for deslorelin (EMEA/MRL/830/02-FINAL), genotoxicity studies are not deemed necessary. In literature, peptidic substances such as deslorelin have not been associated with genotoxicity.

Carcinogenicity

No new data were presented. For Suprelorin 4.7 mg it was concluded that due to the peptide nature of such GnRH analogues, these compounds would not be expected to possess any mutagenic potential.

III.1.4 Studies of other effects

Only one new study was presented. This was a publication in which deslorelin was used in the chemoprevention of breast cancer in humans. The study confirmed expected lack of toxicity in humans.

III.1.5 User safety

The applicant presented a user safety risk assessment conducted in accordance with CVMP guidelines. Use of Suprelorin 9.4 mg is considered to pose the same risks for the user as Suprelorin 4.7 mg and the same user safety warnings have therefore been implemented in the product literature. Pregnant women should not administer the product as GnRH analogues have been shown to be foetotoxic in laboratory animals.

III.1.6 Environmental risk assessment

The applicant presented a Phase I assessment in compliance with VICH GL6. Since the product is for use in dogs only and the administration frequency is as long as 12 months, the environmental exposure is concluded to be minimal. Further assessment is therefore not necessary.

III.1.7 Overall conclusions on the safety documentation

Suprelorin 9.4 mg differs in the pharmacokinetics from Suprelorin 4.7 mg by a slower release rate of deslorelin. This is due to exclusion of sodium acetate in the 9.4 mg formulation.

The safety data presented confirmed the well tolerated use of Suprelorin 9.4 mg in the target animals and that it presented a low risk to the environment. Appropriate user safety warnings have been implemented in the product literature, i.e. pregnant women should not administer the product since foetotoxic effects have been observed in laboratory animals.

IV Efficacy

IV.1 Pharmacokinetics

Refer to Safety section.

IV.2 Pharmacodynamics

No new data were presented for Suprelorin 9.4 mg. In line with Suprelorin 4.7 mg, the applicant used plasma testosterone as surrogate marker for infertility and applied a testosterone threshold of 0.4 ng/ml.

IV.3 Target Animal Tolerance

The applicant presented a target animal safety (TAS) study, safety data from the clinical studies as well as pharmacovigilance data for Suprelorin 9.4 mg implants as authorised in Australia.

The GLP TAS study was conducted with 6x the recommended dose, i.e. 10 implants of 6 mg deslorelin administered at the same time in each of 4 beagle dogs (2M/2F, 13-19 months). While the observation period was three months only, this study was well conducted and confirmed that six times the recommended treatment dose was well tolerated both locally and systemically in the four dogs.

Safety data from the clinical trials also confirmed the well tolerated use of Suprelorin. Safety data from the clinical studies using up to 5 repeated administrations of Suprelorin 4.7 mg were used to confirm safety after repeated administrations of Suprelorin 9.4 mg. This was justified by the fact that while the dose in one Suprelorin 9.4 mg implant is twice that of on Suprelorin 4.7 mg implant, the annual dose is the same, thus the studies were used for assessment of longer-term safety equivalent to 2 repeated implants of Suprelorin 9.4 mg. Furthermore, no new excipients were added in Suprelorin 9.4 mg.

Pharmacovigilance data presented four cases of suspected adverse reactions. They included each of the clinical symptoms lethargy, hives, diffuse alopecia and urinary incontinence. Considering the mode of action of Suprelorin 9.4 mg and the absence of other cases reporting similar adverse events, the incidents were considered as isolated with no need to amend the SPC. One dog presented with CNS symptoms 7-10 days after implantation, but the Suprelorin 9.4 mg was considered unlikely to have caused these clinical signs.

Considering all tolerance data presented by the applicant, the use of Suprelorin 9.4 mg was considered safe. This was confirmed by the considerable overdose of deslorelin used in the target animal study.

IV.4 Dose determination / justification

The initial clinical trials conducted with deslorelin implants indicated that a dose between 6 and 12 mg is appropriate to obtain temporary infertility in healthy, intact male dogs for approximately 12 months.

IV.5 Dose confirmation

A confirmatory non-GCP trial conducted with 25 male dogs (10 male dogs given a single 5.6 mg Suprelorin implant, 10 dogs given a single 9.4 mg implant and 5 dogs given a placebo implant) supported a dose of 9.4 mg to obtain temporary infertility for approximately 12 months. The choice of 9.4 mg as the dose in the final formulation is therefore sufficiently demonstrated.

IV.6 Field trials

The applicant presented one pivotal GLP field trial using the final formulation of Suprelorin 9.4 mg implant in 30 male dogs and a placebo implant in 5 control dogs. The study confirmed the results of the dose finding studies and sufficient evidence was found for suppression of gonadal function for at least 12 months, measured by the surrogate markers of plasma testosterone levels below 0.4 mg/ml and/or a significant reduction in testicular size. The results were not confirmed by attempts for semen collection as was done for Suprelorin 4.7 mg. This is accepted since use of unsuccessful semen collection as supportive evidence for infertility can be questioned. The applicant has proven suppression in 90% of dogs by week 8 whereas some dogs may not be suppressed until approximately week 12. Thirty two per cent of the dogs did not return to normal reproductive potential within 2 years after the treatment and reversion to full fertility has not been fully documented.

Clinical studies conducted with repeated administrations of Suprelorin 4.7 mg provided some support on continuous infertility between repeated implantations. This is addressed in the SPC.

IV.7 Other studies

None.

IV.8 Overall conclusion on efficacy

The choice of 9.4 mg as the dose for induction of temporary infertility in healthy male dogs for approximately 12 months was sufficiently demonstrated in the dose finding studies presented by the applicant.

The pivotal GLP field trial confirmed the results of the initial clinical studies, i.e. sufficient evidence was found for suppression of gonadal function for at least 12 months, measured by the surrogate markers of plasma testosterone levels below 0.4 mg/ml and/or a significant reduction in testicular size. The applicant proved suppression in 90% of dogs by week 8, whereas two dogs were not suppressed until approximately week 12. Thirty two per cent of the dogs did not return to normal reproductive potential within 2 years after the treatment and reversion to full fertility was not fully documented. These data are implemented in the product literature.

Clinical studies conducted with repeated administrations of Suprelorin 4.7 mg provided some support on continuous infertility between repeated implantations.

V Benefit Risk Assessment

Introduction

- Suprelorin 9.4 mg deslorelin implant for dogs
- Extension, new strength resulting in double duration of effect

Benefit assessment

Direct therapeutic benefit

Suprelorin 9.4 mg is an implant for subcutaneous administration in healthy male dogs for temporary suppression of the gonadal function for at least 12 months. For most dogs, suppression is achieved within 8 weeks after implantation.

However, one third of the dogs did not return to normal reproductive potential within 2 years after the treatment and reversion to full fertility was not fully documented. Moreover, use of the product in pre-pubertal dogs has not been investigated. Finally, while the product will reduce the libido of the dog, other behavioural changes (e.g. male-associated aggression) have not been investigated.

Additional benefit

Suprelorin 9.4 mg has a longer duration of effect (12 months) than the existing product (Suprelorin 4.7 mg), i.e. the product should only be administered once a year to maintain a therapeutic effect. Suprelorin 9.4 mg provides a beneficial alternative to permanent intervention procedures, i.e. surgical castration.

Risk assessment

Suprelorin 9.4 mg is well tolerated in the target animals, both locally and systemically. Suprelorin 9.4 mg presents no risk to the environment.

Suprelorin 9.4 mg is a preloaded implanting device intended for use by professional users only and it is considered relatively safe for users to handle the product. However, since deslorelin is able to alter hormone profiles and to elicit reprotoxic and embryotoxic effects at very low doses a contraindication for use by pregnant women is included in the SPC.

Evaluation of the benefit risk balance

Suprelorin 9.4 mg has been shown to have a positive benefit risk balance overall. The product has been shown to be efficacious for the induction of temporary infertility in healthy male dogs for at least 12 months.

It is well tolerated by the target animals and presents no risk for the environment. The user safety is acceptable, provided that use by pregnant women is contraindicated since foetotoxic effects have been observed in laboratory animals. Appropriate warnings are included in the product literature.

Conclusion on benefit risk balance

A positive benefit risk assessment can be reached subject to the agreed post-opinion commitments and with the agreed SPC and product literature.

Conclusion

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP considers that the application for Suprelorin 9.4 mg is approvable.

Based on the original and complementary data presented, it is concluded that the quality, safety and efficacy of Suprelorin 9.4 mg were considered to be in accordance with the requirements of Council Directive 2001/82/EC, as amended.