15 September 2011
EMA/CVMP/730940/2011
Veterinary Medicines and Product Data Management

EPAR Scientific discussion post authorisation for Suprelorin

International Non-proprietary Name: deslorelin acetate

Procedure No. EMEA/V/C/109/II/007

EU/2/07/072/003-004

Scope of the variation: addition of male ferrets as target species for the 9.4 mg Suprelorin implant.

Scientific discussion

Introduction

Suprelorin 9.4 mg was authorised in EU as a line extension to Suprelorin 4.7 mg on 01.07.2010 indicated for the induction of temporary infertility in healthy, entire, sexually mature male dogs with duration of efficacy of up to at least 12 months. The subject of this Type II variation application is the addition of male ferrets, to the existing marketing authorisation for Suprelorin 9.4 mg. The active ingredient is deslorelin, a nonapeptide analogue of gonadotrophin releasing hormone (GnRH).

MUMS classification

The application has been submitted in accordance with MUMS (Minor Use Minor Species) requirements (cf. Guideline on Efficacy and target animal safety data requirements for veterinary medicinal products intended for minor uses or minor species (EMEA/CVMP/EWP/117899/2004)). In February 2010 the Committee for Medicinal Products for Veterinary use (CVMP) discussed the request for MUMS classification for Suprelorin 4.7 mg for ferrets and agreed to classify the product as MUMS since ferrets are a minor species and the indication was considered a minor use.

The medicinal product is intended as an alternative treatment to surgical castration to control skin odour and intraspecies aggressive behaviour in ferrets. There is increasing evidence that surgical castration may precipitate the development of hyperadrenocorticism due to an increased secretion of gonadotropins (LH and FSH). Suprelorin containing the active substance deslorelin is a depot GnRH implant which acts by long term inhibition of the production and release of LH and FSH due to a desensitization of gonadotrophin receptors in the pituitary gland. Consequently, it is considered an alternative to surgical neutering and thereby limiting the development of hyperadrenocorticism in ferrets.

While the original MUMS request concerned Suprelorin 4.7 mg for ferrets, the subject of this application is Suprelorin 9.4 mg implant, an identical formulation to Suprelorin for dogs. The CVMP anticipates that the change in strength is explained by a wish for extended duration of efficacy. This can be accepted provided that appropriate efficacy and safety documentation for the relevant formulation is presented. Pharmacological and toxicological properties of deslorelin in ferrets are not expected to be significantly different from those in dogs and there is extensive experience with the 4.7 mg deslorelin/Suprelorin for dogs.

Part 3: Safety

No significant new data were provided in the original dossier for this part. The applicant has not presented a specific target animal safety study in the ferret, but refers to the data presented for Suprelorin 9.4 mg in the dog, including pharmacovigilance data from dogs in Australia. In addition safety data are available from a clinical study conducted with Suprelorin 9.4 mg in male ferrets.

The data from dogs demonstrated that Suprelorin 9.4 mg was well tolerated, also after long-term use (two or three consecutive implantations). This was confirmed by the considerable overdose of deslorelin (6x) used in the pivotal target animal safety study (Godin 1998, Ref. 5) as well as the pharmacovigilance data presented covering the period from January 2007-May 2009 (Yeates 2009, Ref. 6).

The SPC for Suprelorin 9.4 mg describes the following possible adverse reactions in dogs (Section 4.6), i.e. "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."

Section 4.9 reads: "Studies in dogs showed that no adverse reactions other than those described in section 4.6 have been observed following subcutaneous administration of up to six times the recommended dose."

In the clinical study conducted by Schoemaker (Ref.4) with Suprelorin 9.4 mg in ferrets, no treatment related adverse reactions were reported during the study hence no adverse reactions have been included in the SPC section 4.6. Section 4.10 (Overdose) reads that no data are available in ferrets.

The CVMP considering the MUMS requirements and since the pharmacological and toxicological properties of deslorelin in ferrets are not expected to be significantly different from those in dogs the absence of an ADME study in ferrets and thus the absence of any pharmacokinetic data in the SPC section 5.2 is justified. As was also discussed for Suprelorin 9.4 mg for dogs, for the purpose of this application it is considered that the pharmacological actions of deslorelin are more relevant than its pharmacokinetic properties. Moreover, plasma deslorelin seems to be difficult to assay accurately, due to low concentrations detected in plasma attributed to the slow release of deslorelin from the implant.

The CVMP considers that despite the MUMS requirements and since the pharmacological and toxicological properties of deslorelin in ferrets are not expected to be significantly different from those in dogs no defined safety endpoints were measured. The applicant was asked to justify this absence, explain the type and frequency of adverse reactions and further discuss safety in the proposed target species. In addition to this CVMP was of the opinion that whether this information is considered insufficient the SPC section 4.6 should as a minimum read that limited data are available.

The applicant answered including a reference to an expert opinion by Nico J. Schoemaker included in annex III to support of the use of the Suprelorin implant in ferrets. After the study on male ferrets that was included in this application (Schoemaker et al 2008), Suprelorin implants containing 9.4 mg deslorelin (subject of this application) and 4.7 mg deslorelin both authorised for use in dogs were used in privately owned ferrets. During 2010 a survey was conducted on ferrets that had received the 4.7 mg implant 2 years earlier. The data from this survey shows that only 16 out of 117 (13.7%) evaluated ferrets presented minor side effects after implantation. These included pruritus at the site of placement (duration less than 2 days); local erythema; minor local swelling and a small crust at the site of implant placement. No major adverse event has been highlighted in the Expert Opinion. The Expert concludes that the Suprelorin implant can be safely used with only minimal local side effects at the site of implantation after placement of the implant.

In addition, the applicant has presented a summary of a GCP multi-centric open field study which is currently being conducted in France: "Clinical Efficacy of a 4.7 mg deslorelin implant on reversible long term contraception in male ferrets". The applicant has presented at this stage information that is not considered a preliminary report but only a summary of the data available at this date. Out of the 29 animals in the study no severe abnormal clinical signs were recorded, and only 3 animals presented abnormal clinical signs (1 animal presented slightly granulated faeces, weight increase was observed in one animal and in another animal the implant had broken in two parts). It is difficult to determine the relevance of these adverse events in relation to the use of the implant in ferrets. However, it is reasonable to assume, according to what has been reported previously by Schoemaker, that these are probably isolated events, unrelated to the Suprelorin 4.7 mg implant and could have been caused by changes in animal management (nutrition and behaviour).

In view of the above the applicant proposes to include the following text in Section 4.6 of the SPC: "In ferrets, the following have been described: Transient moderate swelling, pruritus and erythema at the implant site"

The CVMP accepts this wording. The wording of the proposed SPC, Section 4.6 should state the present knowledge on adverse reactions which means that it is difficult to include the correct frequency of single elements.

The CVMP also proposed to reset the periodic safety update report (PSUR) cycle for Suprelorin, in view of the addition of a new target species. Following the submission of the next routine PSUR (covering the period: 01/02/2011-31/01/2012), the first six-monthly PSUR of the reset PSUR cycle would have a data lock point of 31/07/2012. PSURs covering all authorised presentations of the product would be required at 6 monthly intervals for the next two years, followed by yearly for the subsequent two years and thereafter at 3 yearly intervals.

The applicant has provided a user safety risk assessment conducted in accordance with CVMP guideline on the User Safety for Pharmaceutical Veterinary Medicinal Products (EMEA/CVMP/543/03). The risk assessment for the user when treating a ferret has not changed compared to that made for the user when treating a dog. CVMP considers that the addition of ferrets as target species is not expected to cause additional risks for the user compared to the risks when handling/treating dogs. This is supported by the recommendation to administer the implant under general anaesthesia, which reduces the risk of sudden movements hence reducing the risk of accidental self injection. The user safety warnings in the SPC are therefore unaltered.

A Phase I Environmental Impact Assessment has been provided in accordance with the appropriate guidelines. Since Suprelorin 9.4 mg is indicated for non-food producing animals only, the environmental exposure is concluded to be minimal. Further assessment is therefore not necessary and the environmental assessment finishes in Phase I.

Part 4: Efficacy

Preclinical data

CVMP agrees that, as this application concerns authorisation for use in a minor species, no preclinical data in the target species is needed and reference could be made to the data presented for the dog in the original dossier. According to MUMS guideline EMEA/CVMP/EWP/117899/2004 this is acceptable when the product is authorised for the same indication in a major species in which pharmacology is likely to be comparable.

No dose determination study has been conducted in ferrets. According to the MUMS guideline this is acceptable if efficacy of the product at the recommended dose regime is demonstrated in an adequate and controlled dose confirmation study in the target species (cf. the pivotal field study by Schoemaker 2010, Ref. 4). Further, it is highlighted that dosages in ferrets are normally determined empirically based on the knowledge of use of the drugs in other species, in particular the dog. Data are available from clinical practise in ferrets for the indication (veterinary practitioners confirm this).

Clinical data

Pivotal confirmatory study (ref. 4)

Title: Safety and efficacy of a Gonadotropin releasing hormone agonist implant (Suprelorin 9.4 mg) as an alternative for surgical castration in male ferrets

Year: 2005-2006, Department of Clinical Sciences of Companion animals, Faculty of Veterinary Medicine, Utrecht University, The Netherlands

Objective: To investigate the effect of treatment with a depot GnRH-agonist implant containing 9.4 mg deslorelin, on plasma FSH and testosterone concentrations, testes size, spermatogenesis and the odour of intact male ferrets.

Animals: 21 healthy, adult intact male ferrets at the beginning of the breeding season, bodyweight 1.0-1.7 kg, age 1-2 years old.

Design: Non-blinded, randomised prospective longitudinal clinical study. Non-GCP. Three treatment groups, each containing seven ferrets – one negative control group implanted with placebo implant (Group 1), one treatment group implanted with deslorelin implant 9.4 mg (Group 2) and one positive control group with animals surgically castrated on day 0 (March 17 2005). Each animal in group 1 and 2 was implanted subcutaneously with one unit on day 0, skin at injection site sealed with tissue glue (Vet-seal®, B. Braun Medical). All animals in group 1 and 2 had their left testis surgically removed 14 weeks after day 0 (for histological evaluation) using the same procedure as described in group 3.

Product: Suprelorin implant 9.4 mg (Final formulation, Batch no. DR062) and Placebo implant (containing no deslorelin, Batch no. DR051), Peptech Animal Health

Efficacy end points:

Primary:

- Plasma testosterone, LH and FSH concentrations, blood sampled D-7, D0, weekly for eight weeks, followed by every second week from week 10 to week 24 post-treatment (March 10 – September 1, first breeding season) and finally one blood sampling 68 weeks (17 months) post-treatment (July 6 2006)). All substances were measured using radioimmunoassay with a limit of detection for testosterone, FSH and LH of 0.05 nmol/L, 0.8 µg/L and 0.4 µg/L, respectively.
- Total testis volume, right testis, width and length measured at each blood sampling session and testis volume calculated ($width^2$ x length x 0.524) as reported by Wolf et al, 2000 (Ref.7)
- Testis weight and testis histology on left testis surgically removed in group 1 and 2 (week 14), PAS stain, spermatogenesis was scored 1-10 (1=no spermatogenesis, 10=complete spermatogenesis) using the Johnson method (Johnson 1970, Ref. 8) as modified for use in dogs (Peters et al. 2000, Ref. 9)

Secondary:

- Odour (14 weeks after castration or implantation, cotton cloths placed in boxes of all animals and after two nights cloths were collected in individually sealed bags and a test panel (n=83 persons) scored the smell 1-5 (1=no smell, 5=very strong odour). Bags were opened in random order.
- Body weight (measured for all animals at every blood sampling time point)
- Other observations: Adverse reactions not reported. One ferret in Group 1 (no. 9) was diagnosed with hypogonadism and its data were excluded from the efficacy analysis. One animal in group 3 died during insulinoma surgery and one animal in group 1 died from thromboendocarditis. Vaccination during the study against Canine Distemper Virus (Nobivac Puppy PD, Intervet mederland B.V. Boxmeer, the Netherlands)

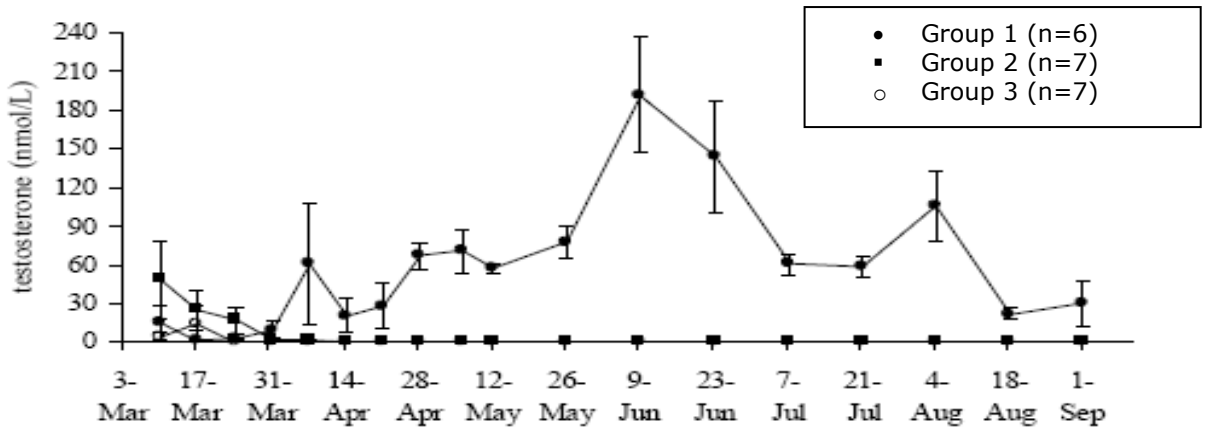
Statistical analysis: SPSS for Windows (Version 12.0) and R (Version 2.2.0). Significance $P<0.05$.

Results:

Plasma testosterone concentrations at D0 (March 17th 2005):

No statistical analysis was performed on the D0 data, but at Day -7 no statistically significant differences was found in plasma testosterone levels between the three groups.

Testosterone levels per group from D-7 to week 24 (Figure 1 of the study report):



Testosterone levels per group 68 weeks (July 6th 2006) after implantation (Table 4 of the study report):

Group 1		Group 2		Group 3	
Ferret no	nmol/L	Ferret no	nmol/L	Ferret no	nmol/L
3	20	12	0.05*	21	-**
4	9.2	13	0.05	22	0.05
5	32	14	0.1	23	0.05
6	69	15	0.05	24	0.05
7	73	16	0.05	25	0.05
8	-**	17	0.05	26	0.05
9	-***	18	0.05	27	0.05

*Limit of detection = 0.05 nmol/L // **Died due to insulinoma surgery respectively thromboendocarditis // ***Withdrawn from study due to hypogonadism

Four weeks after D0 and onwards ferrets in both group 2 and 3 had significantly lower testosterone concentrations than ferrets from the placebo group (P<0.01). Sixteen months (15 months and 3 weeks) after treatment the testosterone concentrations were still significantly lower in both groups (all concentrations <0.05 nmol/L) compared to ferrets in the placebo group (P<0.01: n=5; range 9-73 nmol/L). The testosterone concentrations between Group 2 and 3 ferrets did not differ significantly from each other. Two ferrets in group 2 (no. 12 and 13) had concentrations of 0.2 nmol/L at week 4, the remaining had levels of 0.05 nmol/L. From week 5 and until week 24 and at the assessment conducted 68 weeks after treatment, three of seven ferrets in Group 2 remained at 0.05 nmol/L, whereas levels transiently increased to 0.1 nmol/L (Ferret 14, 15, 16) and 0.2 nmol/L (Ferret 17) at single time points within the study period in the other animals (week 14, 16, 22 and 24). In group 3, testosterone concentrations of 0.05 nmol/L were measured from week 1 and throughout the remaining study period in 5 of 7 animals. In two ferrets (no. 21 and 23) concentrations of respectively 0.7 and 0.5 nmol/L were measured at each of one occasion in week 24 and 22. In the placebo group, varying testosterone concentrations were observed during the first 5 weeks, but from week 6-7 testosterone levels were markedly increased in all animals (14 – 138 nmol/L) compared to the other groups.

Testis volume of the right testis in Group 1 and 2 (Figure 9+10, App. 5 of the study report):

At D-7, no statistically significant difference was found in the testes volume between the groups. From five weeks after implantation and until the end of the study a significant difference in testis size was found between the groups (P<0.01). Sixteen months after treatment testis volume in the deslorelin group (n=7, 0.08-0.15 cm^3) was significantly smaller compared to the testes volume in the placebo

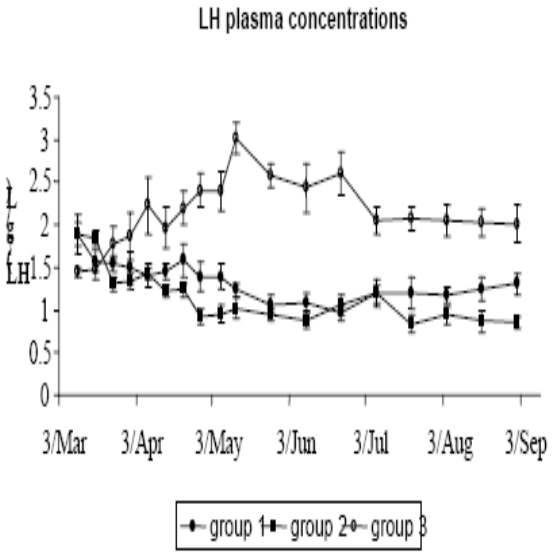
group (n=5, 0.94-1.38 cm^3). A significant correlation was found between the volume of the testis and the plasma testosterone concentration ($p<0.05$).

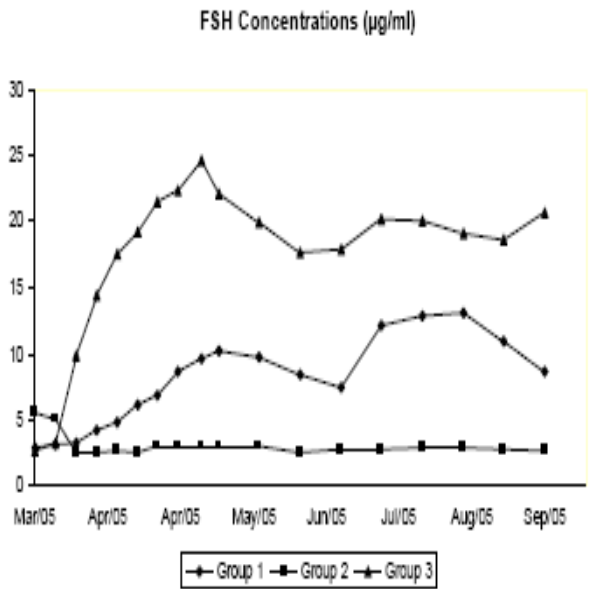
Testes weight and histology (Johnson score) 14 weeks after treatment:

Group 1		Group 2	
Ferret #.	Testis weight (g)	Ferret #.	testis weight (g)
3	2.28	12	0.24
4	1.28	13	0.27
5	2.44	14	0.34
6	2.13	15	0.34
7	2.21	16	0.36
8	1.65	17	0.47
9	-	18	0.25
mean	1.99		0.32
St dev	0.44		0.03

In six of seven placebo animals spermatogenesis was considered normal, i.e. all stages of spermatogenesis were observed. Ferret no. 9 was excluded from the study due to hypogonadism. In the deslorelin group, no normal spermatoginia or spermatocytes could be found in any testes (Johnson score 2 = no germ cells, only sertoli cells present).

LH and FSH plasma concentrations (Figure 2 and 3 of the study report):





Odour in week 14:

Differences in odour were described between all three groups. The strongest odours were found on the cloths from in the placebo group (3.8 ± 0.2), followed by the cloths of the surgically castrated ferrets (3.1 ± 0.1) and the ferrets in the Suprelorin group (2.7 ± 0.1).

Safety: No adverse reactions that could be attributed to treatment were reported during the 16 months of study duration. One animal in group 3 died during insulinoma surgery and one animal in group 1 died from thromboendocarditis.

Conclusion of the pivotal study made by the applicant: The applicant considered that the study demonstrated that the deslorelin implant in ferrets effectively decreased testosterone concentration in blood to a level comparable to levels in the ferrets that had been surgically castrated. Furthermore, testis size was significantly decreased in ferrets in the deslorelin group in comparison to the ferrets in

the placebo group and testicular histology in week 14 showed no sign of spermatogenesis in the testis of the ferrets treated with the deslorelin implant. The characteristic musky odour of male ferrets was also decreased in the ferrets that were treated with the deslorelin implant in comparison with the placebo and surgically castrated groups. FSH and LH concentrations were also decreased in the ferrets in the deslorelin implant group compared to the surgically castration group.

The CVMP is of the opinion that this non-GCP study confirms the suppression of the normal sexual potential of male ferrets implanted once with the final formulation of Suprelorin 9.4 mg. It is a confirmatory study more than a traditional field study since it was performed at one site only. The fact that the study was conducted non-blinded is less important since the primary end points, e.g. plasma testosterone concentration and testis volume, are objective.

It should be noted that the study was initiated at the beginning of the breeding season, thus the plasma testosterone concentrations were low in all treatment groups at D0. Gonadal activity is seasonal in ferrets (both in male and female ferrets) and light (more than 12 hours of day light) plays a crucial role in the promotion of reproductive activity (Schomaker et al., submitted[1]). The length of the breeding season therefore depends on the weather and geographical location. For this study it was expected to start in March and end in September.

Allocation to treatment group

According to Schoemaker et al. 2008 (Ref. 3) allocation to treatment group was randomised but CVMP considered that method is not further explained. The applicant was requested to do that, especially since the plasma testosterone levels vary considerably between treatment groups at D0. After further explanations in the LOQ the method of randomisation for allocation to treatment group was considered acceptable and the point resolved. The submitted study protocol for this pivotal clinical study is considered acceptable.

Limit of detection for testosterone

It was noted that the limit of detection was lowered from 0.2 nmol/L to 0.05 nmol/L without any further explanation and no validation of the assay has been provided. The applicant was asked to provide a further explanation. In this explanation applicant argued that it is accepted that a commercially available radioimmunoassay kit was used to analyse the testosterone data, so the test was validated and peer reviewed and accepted by the scientific community when used in this study. As the clinical relevant threshold for infertility was set to 0.1 ng/ml even the first established limit of detection (0.2 nmol/0.06 ng/ml) covered the lower margin of the measured testosterone levels. CVMP considers that although applicant does not explain why limits of detection increased from 0.2 nmol to 0.05 nmol during the study in the commercially used testosterone kit, it is accepted that this fact does not quantitatively affect the obtained results.

Number of animals included in the study and stage in the reproductive cycle

The CVMP also observed that the number of animals included in this study was not justified and although the application is categorised as MUMS, the number of test subjects is limited. Of special concern is the placebo group, in which the testosterone levels vary considerably throughout the study period and the number of animals is reduced to only five at the end of study. The applicant was asked to justify the number of animals included in the study and discuss, if seven ferrets per group can be considered representative for the target population, in particular with regard to the high intra- and intervariability in testosterone concentrations and timing of implantation in relation to age of the animals (1-2 years) as well as stage in the reproductive cycle (early in the breeding season). SPC amendments should be considered accordingly. As a minimum the SPC should address the stage in the reproductive cycle at which animals should be treated.

The applicant answered that Schoemaker study was conducted to determine the efficacy of the Suprelorin 9.4 mg deslorelin implant in ferrets as an alternative to surgical castration. Groups of 7 animals were considered statistically sound for the conduct of the study and this justification was accepted by the Animal Experiment Committee of the Faculty of Veterinary Science in Utrecht.

The applicant presented Parts A, B and C of the application for the ethical examination of the use of laboratory animals containing detailed information on the study plan. Part B Section 8 describes the methodological measures (study design, statistics) that have been taken to calculate and limit the number of animals. The following information was submitted: "6 animals is the minimum in order to be able to use reliable statistics. As natural loss cannot be ruled out, 7 animals per group were chosen to ensure certainty.

The statistical differences found during the study were clearly significant; therefore the number of animals included in the study has been demonstrated to be adequate.

The variation in testosterone levels was seasonally dependent, which is normal for ferrets and the variation in testosterone concentrations between the animals during the study were not considered to be dramatic by the investigator. The implant was placed at the beginning of the breeding season to allow full monitoring of the entire breeding season for the placebo group. Although it would have been advisable to administer the implants later on in the breeding season so that full effect could be monitored (decrease in testosterone concentration-decrease in testis size), this issue was not identified at the start of the study.

In addition, the applicant was currently conducting a GCP multi-centric open field study in France: "Clinical Efficacy of a 4.7 mg deslorelin implant on reversible long term contraception in male ferrets". The applicant has presented at this stage information that is not considered a preliminary report but only a summary of the data available at this time (See Annex 1). The objective of the study is to evaluate the efficacy and tolerance of the 4.7 mg deslorelin implant in male ferrets. Inclusion criteria determined for this study was based on what had been reported by Schoemaker et al; therefore, all ferrets included in this study were required to be in "in rut", i.e. observable sexual behaviour. Healthy, male, intact ferrets between 6 and 33 months were selected for the study. Although this study is still ongoing, preliminary data show that on a visit on day 45 after implant placement 29 out of 29 ferrets were considered to be sexually inactive and only 2 presented musky odour. Testosterone levels were below 0.1 ng/ml for all ferrets, except in two ferrets where testosterone levels were 0.3 and 0.4 ng/ml. However, all animals were recorded as sexually inactive. In a further visit approximately 56 days after treatment the two ferrets that initially presented with testosterone values above 0.1 ng/ml had values below 0.1 ng/ml. The study appears to show that levels of testosterone below 0.1 ng/ml are found in ferrets that present no signs of sexual behaviour. Animals included in this study, although conducted in the reproductive season, also exhibit variation in testosterone levels on D0 ranging between <0.1 to 25.5 ng/ml (See Annex 2 Tables) without affecting the overall effect of deslorelin on testosterone and sexual behaviour. Similarly, although for this study implants were administered during the breeding season, it is apparent that the effect achieved regarding testosterone levels and testicular size was comparable to that reported by Schoemaker et al in the study where the deslorelin implant was administered at the beginning of the breeding season.

Regarding the age of the ferrets to be treated with the deslorelin implants, animals for the Schoemaker study were 1 or 2 years of age, while animals in the on-going field trial are between 6 and 33 months of age. It has been reported that sexual maturity is reached in ferrets at approximately 6 months. Therefore, the SPC should indicate that Suprelorin 9.4 mg implant should be administered to animals older than 6 months that have reached sexual maturity.

In view of the additional information presented at this stage the Applicant has amended Section 4.5 of the SPC as follows (see comments in the SPC):

"Ferrets

The use of the product in pre-pubertal ferrets has not been investigated. It is therefore recommended that ferrets should be allowed to reach puberty before treatment with the product is initiated.

Treatment in ferrets should be initiated at the beginning of the breeding season.

The safety after repeated implantations with Suprelorin in ferrets has not been investigated."

The CVMP accepted the data from the ongoing field study to bring further support to the data from the original application thereby increasing the robustness of results to be representative for the target population of ferrets. Although no placebo controls were included in this study, these data indicate that ferrets in rut can be "chemically castrated" to an acceptable testosterone level equal to the testosterone level for surgically castrated ferrets or ferrets outside the breeding season. The wording proposal to be included in the SPC, Section 4.5 is reasonable and acceptable.

Onset of infertility and duration of efficacy:

The applicant claimed infertility from 4 weeks and up to at least 16 months after implantation of Suprelorin 9.4 mg. Results clearly show an effect of deslorelin on sexual suppression over the study period compared to the placebo group. However, no clinically relevant threshold value for infertility has been set or discussed.

The histology results at week 14 clearly show that halfway through the study the animals are infertile, but it seems difficult to assess onset of infertility as well as duration of efficacy from the data presented. Statistically significant differences between placebo- and deslorelin treated animals do not explicitly imply that the animals are infertile and raw data show that the testosterone levels in some ferrets in the placebo group were still low after week 4 (e.g. Ferret no. 4 having levels of 0.4 and 0.8 nmol/L in week 4 and 5). This may leave the question if the low testosterone levels in the Suprelorin group (as well as in the surgically castrated group) are explained by treatment or by the fact that some animals are still naturally infertile at this early stage in the breeding season.

Furthermore, in regard to duration of efficacy only one efficacy assessment were made after week 24, i.e. in the second breeding season after implantation. Taking the limited number of animals (especially in the placebo group, n=5) into consideration as well as the varying testosterone levels in the placebo group and the absence of a threshold value for infertility, at present data appear too sparse to conclude on duration of efficacy. This is confirmed in the paper by Schoemaker et al. 2008 (Ref. 3), in which the author/study investigator concludes that further studies are necessary to determine the duration of efficacy of the deslorelin implants in ferrets.

The applicant was required to discuss a clinically relevant threshold value for infertility in ferrets (or justify the absence) and elaborate a proposal of onset of infertility and duration of efficacy after implantation of Suprelorin 9.4 mg.

See pages 14 and 17 for applicant responses and CVMP point of view about this point

Return to normal fertility after end of treatment:

Return to normal plasma testosterone levels following implantation and the ability of hobs to produce offspring following this return were not studied. This is acceptable as it is stated in the SPC and considering the limited requirements for MUMS products. In dogs, 95% of animals treated with Suprelorin 9.4 mg returned to normal plasma testosterone levels within 2.5 years of implantation. However, data for dogs of less than 10 kg were limited and clinical trials with Suprelorin 4.7 mg showed that the mean duration of testosterone suppression was 1.5 times longer among these smaller size dogs compared to larger dogs. It is unknown if the data can be extrapolated to ferrets. Nevertheless, the CVMP suggested the following amendment of the SPC text (section 4.4), i.e. "The

return to normal plasma testosterone levels following implantation and the ability of hobs to produce offspring following this return, has not been investigated. Therefore, the use of Suprelorin should be subject to a risk/benefit assessment performed by the responsible veterinarian".

See pages 14 and 17 for applicant responses and CVMP point of view about this point

Continuous infertility between repeated implantations:

Based on data from the dog, the applicant claims that efficacy is maintained, provided that the product is administered every 16 months (SPC section 4.4). Due to the MUMS classification, the extrapolation of data from dogs can be accepted, since these data were convincing and we have no reason to believe that significant differences would be seen in ferrets. However, the statement may need revision pending the outcome of the discussion on the duration of efficacy.

While sparse, data do not indicate that any of the seven deslorelin treated ferrets lost their implant during the study period as was seen in some treated dogs in the field studies presented in the original dossier for Suprelorin 9.4 mg. One reason may be that the skin at the injection site was sealed with tissue glue. It will be stated in the SPC that tissue glue can be used as a recommendation. The SPC also recommends that the product is administered under general anaesthesia. While general anaesthesia was not used for implantation in this study, the recommendation appears rational, since it leaves time to place the implant properly. The anaesthetic procedure is not expected to influence the performance of the product.

Yet in case a treated ferret loses the implant this may be confirmed by observing an increase in testis size and/or an increase in plasma testosterone levels (i.e. due to the positive correlation between testis volume and testosterone). The applicant was requested to describe how owners can observe these changes and consider if appropriate SPC guidance is needed.

See pages 15 and 16 for applicant responses and CVMP point of view about this point

Summary of Applicant's response about the onset of infertility and duration of the efficacy, return to normal fertility after end of the treatment, continuous infertility after repeated treatments and lose of the implant

Testosterone values in ferrets have been reported in the published literature. Rieger et al conducted a study in 7 male ferrets during the breeding season in July (breeding season starting in March). The study showed that concentrations of testosterone varied in each animal between 2.3 to 25 ng/ml, with mean values of 6 ng/ml to 15 ng/ml. Samples were taken in male ferrets after testosterone values had peaked and were beginning to decline. Neal et al evaluated ten male intact ferrets and one castrated ferret, the animals were housed outdoors and monthly blood samples were collected to measure testosterone concentrations, in addition testis size were measured during one year. The study showed that plasma testosterone concentrations were very low from the end of August to the end of December, with 86% of the plasma samples containing less than 5 ng/ml of testosterone. By the end of February to the end of July testosterone concentrations were always greater than 15 ng/ml with individual peaks on 60 ng/ml declining suddenly at the end of the breeding season at the end of July or August. The plasma testosterone concentrations for the castrated male were always below the sensitivity of the assay (25 pg). In addition, Neal et al measured the testis of male ferrets and showed that the smallest testis length was found in October, and the mean peak testis length in April. Furthermore, a high correlation was found between testis size and plasma concentrations of testosterone through the annual cycle. The relation between testis size and testosterone concentration is a recognised parameter for the evaluation of sexual activity in this species in this field of investigation. A paper published in 2000 studying reproductive ageing of ferrets by Wolf et al, states that seasonal changes in testicular volume and testosterone concentrations is well-established in ferrets. Wolf summarises the following results from previous published studies: Domestic ferrets and

black-footed ferrets are seasonal breeders, with reproductive activity being triggered by a long-day photoperiod. Testes size in black-footed ferrets exposed to natural light increases from December, is maximal from March through May, and decreases thereafter. Additionally, Wolf studied testosterone concentrations in male ferrets of different ages, showing that mean serum testosterone levels were statistically similar in males of 1–5 yr of age and lowest in 6- and 7-yr-old males; Wolf also described variability among males within groups for testosterone levels (i.e., range in 1-yr old males, 0.2–36.1 ng/ml; in 2-yr-old males, 1.3–41.0 ng/ ml; in 3-yr-old males, 0.4–42.0 ng/ml; in 4-yr-old males, 1.2–33.8 ng/ml; in 5-yr-old males, 1.3–47.6 ng/ml; in 6-yrold males, 0.7–30.0 ng/ml; and in 7-yr-old males, 0.5–7.5 ng/ml).

In addition to the study conducted in male ferrets with the 9.4 mg deslorelin implant by Schoemaker, the applicant is currently conducting a study with the 4.7 mg deslorelin implant in ferrets. Suprelorin 12, the implant containing 9.4 mg of deslorelin for use in dogs (subject of this application) was originally authorised as a line extension of the previously authorised Suprelorin 4.7 mg implant for use in dogs. Both implants have the same pharmacodynamic and pharmacokinetic properties and *in vitro* data presented to describe the differences in release between both implants showed that the deslorelin release profiles of Suprelorin 12 and Suprelorin 4.7 mg were qualitatively very similar, but quantitatively the daily release of deslorelin is greater in Suprelorin 12 as it contains more deslorelin. The only difference between both implants in dogs is on duration of effect. In view of this, the applicant considers that additional preliminary data obtained with the 4.7 mg deslorelin implant can be presented in support of these responses.

A GCP multi-centric open field study is being conducted in France: "Clinical Efficacy of a 4.7 mg deslorelin implant on reversible long term contraception in male ferrets". The applicant has presented at this stage information that is not considered a preliminary report but only a summary of the data available to this date (see Annex 1). The objective of the study is to evaluate the efficacy and tolerance of the 4.7 mg deslorelin implant in male ferrets. Twenty nine male ferrets exhibiting signs of sexual activity, i.e. "in rut" were included in this study. Healthy, male, intact ferrets between 6 and 33 months were selected for the study. At the time this summary was prepared, all animals were administered the implant on D0 and two of the five scheduled visits have been conducted. Visit 1 was on D0 and Visit 2 and 2bis were conducted approximately on D42 and D56, respectively. During visit 1 clinical examinations were conducted, samples were collected for haematology and biochemistry and the implants were administered. On visit 2 clinical examinations and blood samples were collected. Further visits (3, 4 and 5) will be conducted at the end of the first breeding season, middle of the second breeding season and at return to sexual activity after treatment and will all consist of clinical examinations and blood sample collection.

Animals included in this study although "in rut", also exhibited a variation on testosterone levels on D0 as described in the publications discussed above (See Annex 2 Tables). Mean testosterone values on the day the implant was placed (D0) were 11.5 ng/ml (range 0.1 – 26 ng/ml) and the median testosterone value was 13 ng/ml. Only 2 of the 29 evaluated animals had testosterone concentrations below 1 ng/ml (0.4 ng/ml and <0.1 ng/ml). On the second visit, on day 45 after implant placement 29 out of 29 ferrets were considered to be sexually inactive. Except for two animals where testosterone levels were 0.3 and 0.4 ng/ml, all animals were below 0.1 ng/ml and all animals were recorded as sexually inactive. Minimum, maximum and median values on this occasion were <0.1, 0.4 and <0.1 ng/ml respectively. In an additional visit approximately 56 days after treatment the two ferrets that initially presented testosterone values of 0.3 and 0.4 ng/ml had values below 0.1 ng/ml. The study appears to show that levels of testosterone <0.1 ng/ml inhibit sexual behaviour in ferrets.

In the Schoemaker study, testosterone concentrations have been now presented in ng/ml to facilitate the comparison between studies (i.e. nmol/L x 0.288) (See tables in Annex 2). The results in the Schoemaker study show that ferrets at inclusion had variable and low values across all groups as it has

been correctly pointed out. However, although on D-7 and D0 testosterone values were low and the groups where not balanced, the difference in testosterone concentrations between the placebo group and both the implant and castrated group becomes evident between week 4 and 5 post treatment and continues throughout the study. The variations in testosterone concentrations found in this study on D-7 and D0 and in the placebo group are consistent with what has been reported in the published literature; nevertheless the low testosterone levels found in the surgically castrated and implant treated groups throughout the study are indicative of inhibited sexual activity in both groups.

Testis size was evaluated in the two studies described above. Both studies showed that testis size decreased, as reported in the published literature, in correlation with the decrease in testosterone levels. In the 4.7 mg study the measurement of the testicular volume on visit 2 (approximately day 45 after treatment) showed a decrease in size between 20% and 90% of the testicular volume in comparison to D0 with a mean value of 78% decrease in testicular size. This was also shown in the Schoemaker study, where the size of the testis was significantly reduced in the group that had been treated with the deslorelin implant, in comparison to the placebo group, from five weeks after implantation until the end of the study. In the Schoemaker study a comparison between the testis size on D0 and in the weeks post treatment in the implanted group was not conducted. Although a decrease in size was also observed with time it was not as noticeable as in the 4.7 mg on-going study, probably due to the relatively low testosterone concentrations at the start of the Schoemaker study where the ferrets included were not confirmed as sexually active. However, when comparing testis size on D0 to testis seize on week 5 (where a significance difference was first noted between the placebo and the deslorelin implant group), testis size in the Suprelorin implant group had decreased on average 34% (range 6 to 65%).

In conclusion, in male intact ferrets, testis size is correlated with testosterone concentrations and this has been supported by findings in recent studies and data available in the published literature. Testosterone concentrations in ferrets are variable and even during the breeding season some animals can be expected to present low values (i.e. 0.2 ng/ml). At this stage, an established threshold value for infertility regarding testosterone concentration in the ferret has not been reported. However, the data reviewed show that surgically castrated ferrets as well as intact male ferrets that have been treated with the deslorelin implant present testosterone levels which are either below the limit of detection or well below 0.1 ng/ml. In addition, the correlation between testis size and testosterone levels in ferrets may also prove a valid parameter to evaluate sexual activity in ferrets as discussed in the Expert Opinion presented in these responses. (See Annex 3)

The applicant has presented an Expert Opinion prepared by an Expert in this field, Nico Schoemaker. The Expert Opinion is included in Annex 3 of these responses. After conducting the study with the 9.4 mg deslorelin implant as presented in this application, the Expert has used the different Suprelorin implants available for use in dogs containing 4.7 mg and 9.4 mg deslorelin in privately owned ferrets. Although this information is yet to be published, in 2010 the Expert conducted a survey among the owners of the ferrets that had been administered the 4.7 mg deslorelin implant two years before. These data are currently being collected as the basis for a future publication. Duration of effect was evaluated by the owners based on odour of the ferrets or increase in testis size. In the surveyed male ferrets the 4.7 mg implant was active at least between 1 and 3 years (on average 2 years). The duration of effect reported by Schoemaker for the 4.7 mg implant was based on the owner's assessment on increase in testis size or odour of the ferrets and was reported in a range of 301 to 1339 days with a median value of 760 days. The Expert also states that duration of effect was increased in ferrets implanted with the 9.4 mg deslorelin implant in comparison to the 4.7 mg according to the owner's observation and that based on the data available in dogs the duration of the 9.4 mg implant is likely to be twice as long as that reported for the 4.7 mg implant.

The duration of effect was only studied until week 68 post treatment in the Schoemaker study presented with this application. The study shows that the level of testosterone in the deslorelin implant group was as low as for the surgically castrated group (no significant difference between surgically castrated and deslorelin implant groups) and significantly lower in comparison to the placebo group. Even though the number of ferrets had decreased in both placebo (n5) and surgically castrated (n6) groups, testosterone concentrations found in each of these groups, placebo (sexually active) and surgically castrated (sexually inactive) are representative of their sexual status, therefore it is considered that they were satisfactory for comparison with the implant treated group.

In view of the above presented information, onset of effect was evaluated in the Schoemaker study, showing a complete onset of effect at Week 5 after implant placement. Although testosterone levels were significantly lower in the deslorelin implant group in comparison to the placebo at week 4 after implantation, a significant difference in testicular size between the implant and the placebo group was not observed until week 5 after treatment. Therefore, this provides a more comprehensive indication of effect evaluating both testosterone concentrations and testis size. Duration of effect has been demonstrated for at least 68 weeks (16 months) after application of the implant (no significant difference between the implant and surgically castrated groups and significant difference between the implant and placebo group). However, further investigations by Schoemaker demonstrate that the duration of effect of the 9.4 mg implant could be considerably longer. In view of the above, it can be considered that termination of effect will be demonstrated by increase in testis size in male ferrets with the corresponding increase in blood testosterone concentrations.

Regarding the above, the wording of the SPC has been modified as follows:

Section 4.4 Special warnings (ferrets)

"Ferrets

Infertility (suppression of spermatogenesis, reduced testis size, levels of testosterone below 0.1 ng/ml, and suppression of musky odor) is achieved from 5 weeks up to 14 weeks after initial treatment under laboratory conditions. Treated ferrets should therefore still be kept away from jills on heat within the first five weeks after initial treatment.

Levels of testosterone remain below 0.1 ng/ml for up to 16 months. Not all parameters of sexual activity have been tested specifically (seborrhoea, urine marking, and aggressiveness). Any mating that occurs more than 16 months after the administration of the product may result in pregnancy.

The need for subsequent implantations should be based on the increase in testis size and/or increase in plasma testosterone concentrations and return to sexual activity.

The reversibility of effects and ability of treated hobs to produce offspring subsequently has not been investigated. Therefore, the use of Suprelorin should be subject to a benefit/risk assessment performed by the responsible veterinarian.

In certain cases, the implant may be lost from a treated ferret. If loss of the implant is suspected in connection with the first implantation, this can be confirmed by observing no reduction in testis size or plasma testosterone levels as both should reduce under correct implantation. If loss of the implant is suspected following re-implantation, a progressive increase will be seen in testis size and/or plasma testosterone levels. In both of these circumstances a replacement implant should be administered."

CVMP point of view after responses about the onset of infertility and duration of the efficacy, return to normal fertility after end of the treatment, continuous infertility after repeated treatments and lose of the implant

The applicant submitted three published papers and data from one ongoing study to support the robustness of the original data submitted and the claims for the proposed SPC in ferrets (MUMS product). The Suprelorin implants with 4.7 mg and 9.4 mg had the same pharmacodynamic and pharmacokinetic properties in dogs, and the release profiles were qualitatively very similar, but quantitatively the daily release of deslorelin was greater from the 9.4 mg implant in dogs leading to twice the duration of effect for the high dose implant (4.7 mg =>6 months versus 9.4 mg =>12 months). As the mechanism of action is very general across animal species for Suprelorin (a GnRH agonist) it is accepted, that the submitted data obtained with 4.7 mg deslorelin implant in ferrets can present support to the original data submitted with the 9.4 mg deslorelin implant in ferrets. The new data represents a worst case situation for the product with expected shorter duration of effect than for the high dose implant.

The applicant provided further support in order to establish a clinically relevant testosterone threshold value for infertility in ferrets as requested by the CVMP. An ongoing GCP multi-centric field study evaluated the clinical efficacy of a 4.7 mg deslorelin implant on reversible long term contraception in male ferrets. Levels of testosterone below 0.1 ng/ml was shown to correlate to inhibition of sexual behaviour in the ferrets, therefore this threshold seems relevant to demonstrate sufficient clinical effect of the Suprelorin implant.

The applicant also provided evidence on the close correlation between plasma levels of testosterone and testis size in ferrets from literature and an ongoing study on the efficacy of Suprelorin 4.7 mg implant. Both indicators are therefore relevant in order to establish onset of infertility and duration of effect for the implant in ferrets.

It is acknowledged that there is a natural variance in the circulating levels of testosterone in ferrets both due to episodic fluctuation caused by the pulsatile release from the testis and due the fact that these animals have only one annual reproductive cycle. The natural variance in testosterone levels is present in the individual ferret during the reproduction cycle as well as between animals at the same time point of the cycle. Results from the ongoing field study (29 male ferrets in rut when the implant was administered) bring support to the onset of infertility from 5 weeks. Duration of effect cannot yet be supported from this study as data still are awaited from the end of the first breeding season, middle of the second breading season and return to sexual activity after treatment (data from clinical examinations and blood samples for plasma testosterone analysis). As duration of effect was demonstrated in the original data for at least 68 weeks (16 months), it is accepted to include this time point as basis in the SPC text, although the duration of effect for the 9.4 mg implant could be considerably longer. The applicant's SPC modifications to Section 4.4 "Special warnings" seem relevant and appropriate. The CVMP agreed to include a reference in the SPC about the recommendation of using tissue glue and explaining how a loss of the implant could be observed by the owner and which actions should be followed afterwards.

The SPC Sections 4.4, 4.5 4.6 and 4.9 and the related in the leaflet have been amended accordingly including the necessary changes.

3. Benefit-risk assessment

A positive risk benefit assessment can be made for Suprelorin 9.4 mg implant for ferrets as it offers an alternative treatment to surgical castration for induction of infertility in ferrets.

4. Overall Conclusions of the evaluation and recommendations

The CVMP considers that this variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, is approvable.

The CVMP also proposed to reset the PSUR cycle for Suprelorin.

Changes to the community marketing authorisation

Changes are required in the Annex I and III of the marketing authorisation.