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Veterinary Medicines Division

Committee for Veterinary Medicinal Products

CVMP assessment report for a type II variation for Suprelorin (EMEA/V/C/000109/II/0032/G)

INN: deslorelin acetate

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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1. Introduction

1.1. Submission of the variation application

In accordance with Article 7 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, Virbac S.A. (the applicant), submitted to the European Medicines Agency (the Agency) on 28 May 2021 an application for a grouped type II variation for Suprelorin.

1.2. Scope of the variation

Variations requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II
C.II.1	C.II.1 - Variations concerning a change to or addition of a non-food producing target species	II

The variation is to add a new therapeutic indication: For the induction of temporary infertility and to delay the first oestrus and heat signs, and to prevent pregnancy at a young age in intact and healthy sexually immature female dogs; and to add a non-food producing target species: For the induction of temporary infertility and suppression of urine odour and of sexual behaviours such as libido, vocalisation, urine marking, and aggressiveness in intact male cats from 3 months of age. In addition, the marketing authorisation holder took the opportunity to implement editorial changes in the product information and to update the local representative for Northern Ireland.

1.3. Changes to the dossier held by the European Medicines Agency

This application relates to the following sections of the current dossier held by the Agency:

Part 1, Part 3 and Part 4

1.4. Scientific advice

The applicant received scientific advice from the CVMP on 19 April 2018 (EMA/CVMP/SAWP/93504/2018).

The scientific advice pertained to the clinical development relating to the appropriate target animal safety studies for the proposed target species female dogs and male cats. The scientific advice has largely been followed and incorporated in the conduct of the studies, except for the proposal to waive the 5x dose group in the dog TAS study, which was maintained due to a requirement from a non-EU regulatory authority. Furthermore, the applicant was informed that the follow-up after the last implantation was deemed very short by CVMP, and it should therefore be clearly stated in the SPC, that reversibility of the effects of the treatment has not been evaluated. The scientific advice also recommended that the applicant should consider recommending the use of appropriate tests in the SPC (e.g. measurement of hormonal levels, vaginal smears) to be sure that each candidate female dog is not close to sexual maturity at the time of implant.

1.5. MUMS/limited market status

Not applicable.

2. Scientific Overview

2.1. Safety (toxicology, user, environment)

Two **acute toxicity GLP studies** in rats were conducted with the IVP in preparation for a non-EU dossier: An acute oral and an acute subcutaneous toxicity study performed in accordance with OECD 423 and 404. Both studies concluded that the LD50 value for both routes of administration was >2000 mg/kg in female CRL:(WI) rats – providing an indication of the level of toxicity of the active substances. However, it should be mentioned that as the product is packaged in single-use devices, the risk of substantial overdosing is unlikely. Furthermore, such LD50 studies are not needed according to EU guidelines.

Since the product is restricted to only being handled by veterinary professionals and the variation encompasses no differences in handling of the product, the current **user safety** text is acceptable.

An **environmental risk assessment** conducted in accordance with the relevant VICH and EMA guidelines has been provided. As Suprelorin is intended for use in dogs and cats, i.e. non-food animal species, the ERA can stop at phase I, question 3 and a phase II assessment is not required. Suprelorin is not expected to pose a risk for the environment when used according to the SPC recommendations.

2.2. Efficacy

2.2.1. New therapeutic indication in dogs

The proposed new indication for dogs is "For the induction of temporary infertility to delay the first oestrus and heat signs, and to prevent pregnancy at a young age in intact and healthy sexually immature female dogs". In support of the indication, the applicant provided the results of one target animal safety and one clinical field study and a summary of follow-up data from female dogs that completed the clinical field study.

The target animal safety study was performed as a randomised blinded and negative-controlled laboratory study with 32 purpose-bred intact female (n = 16) and intact male (n = 16) beagle dogs approximately 12 weeks (84 ± 4 days) old at first treatment. They were randomised into four groups, with four animals per sex per group: group 1 (0X, control), group 2 (1X dose, low dose), group 3 (3X dose, mid dose), and group 4 (5X dose, high dose). The dogs were acclimated for 14 days prior to first treatment.

First treatment was on day 0, the second treatment was at approximately six months (day 182) and the third treatment at approximately 12 months (day 364) after the first treatment. All dogs received five injections at each timepoint. Therefore, the animals in groups 2 and 3 received at each timepoint one or three implantations of the product and four or two injections of the control article, respectively.

Clinical observations were performed on each treatment day, prior to treatment and at approximately 15 minutes, one hour, and two hours after treatment for evidence of adverse

reaction to the treatment. Thereafter, a detailed clinical observation was conducted at monthly intervals until study termination. Clinical observations, food consumption, body weights, rectal body temperature, physical exams, neurological exams, injection site observations, were performed throughout the course of the study. Growth plate assessment via radiography and bone mineral density evaluation via dual energy x-ray absorptiometry (DEXA) scans were also performed. The following samples were collected throughout the study: blood for deslorelin, testosterone, progesterone, haematology and biochemical analysis and urine for urinalysis as well as vaginal swabs for cellular evaluation of oestrus.

Abnormal grand mal seizures were observed in two dogs (female and male), both in group 4 (5X dose) when they were moved from their cage to scheduled examinations. The male dog showed seizures on day 182 prior to the second treatment and on day 189 (one week after treatment). In the female dog seizures were observed on day 268, 301, and 330. Both dogs were examined by a neuropathologist and via neurohistopathology, and no findings that could explain the occurrence of seizures were found.

Other clinical observations/adverse events were recorded, which were all transient and occasional. These adverse events included: eye(s) redness, intermittent ocular discharge, enlarged popliteal lymph nodes, red skin, umbilical hernia, spinning (behaviour), redness and scabbing of skin, vomiting, lumps under injection sites and undescended testicles (pharmacological effect). These observations were considered not to be related to the IVP except for the lumps under the injection site, which is mentioned in section 4.10 (Overdose) of the product information, and undescended testicles.

No effects of the veterinary medicinal product on body weight, food consumption, rectal temperatures, respiratory rate, or heart rate during the physical examination were found. During neurological examination, all animals in the control and treated groups were found to be normal for all parameters assessed.

Several injection site reactions such as presence of blood, redness, swelling, lump(s), irritation, dermatitis, and rash were reported after all three treatments/implantations. Even though the injection site reactions were also observed in the control animals and at injection sites administered saline, the incidence was higher in the IVP-treated animals. The most frequent reactions were swelling and scab, which are mentioned in the section 4.6 (Adverse reactions) of the product information.

All four control females showed evidence of oestrus cycling after day 210 based on vaginal cytology and progesterone analysis. None of the female dogs in the IVP-treated groups (1X, 3X and 5X the recommended dose) exhibited any evidence of oestrus cycling.

Treatment-related effects were limited to a lower bone mineral density at day 390 in males in group 4 (5X dose). A delay in the closure of the proximal physis of the humerus in all treatment groups and a delay in the closure of the distal physis of the femur in males in group 3 and 4 (3X and 5X dose, respectively) was observed.

Alkaline phosphatase was statistically significantly increased in female animals in all treatment groups and increased on most sampling dates in males in all treatment groups beginning on day 28 through day 392 as well.

The reproductive organs in both sexes in animals treated with the investigational veterinary product (IVP) were smaller compared to control animals and compared to what is considered normal at that age. During necropsy, hypoplastic uteri, uterine horns and cervixes of all IVP treated animals and in one dog in group 1 (control) were noted. Histological examination of the

reproductive organs revealed that there was atrophy/hypoplasia in all IVP treated animals.

During necropsy, the injection site was examined for remains of implants, which were found in animals in all three treatment groups. In some cases, the number of implants remains exceeded the number of injected implants, which indicates, that the implants may, in some cases break down to smaller pieces. This could have an impact on the release of the active substance and thereby on the pharmacokinetic in those animals. The individual plasma concentrations of deslorelin showed a big variation within all three treatment groups with a two- to three-fold difference between the animals with the highest and lowest plasma concentrations, which suggests a substantial variation in the release of the active substance from the implant.

Microscopic evaluation of the animals' brains revealed no definitive IVP-related effects. There were no abnormalities identified in the brain from any animals in the 3X and 5X dose groups. One animal in the 1X dose group (group 2) had bilateral focal areas of gliosis (including microgliosis and astrocytosis) and vacuolation in the caudate nucleus (basal nuclei/striatum), the latter of which were not present (and not expected to occur) in concurrent control animals. As this was observed only in one animal in the low dose group (1X dose), this finding was not considered to be related to the IVP.

No samples could be analysed for the first six months of the study due to a lack of a validation method, which is why only deslorelin acetate levels for the day prior to second and third treatment and from days 7, 14, 21 and 28 after the second and third treatment were included in the present submission.

Six months after the first implantation (day 181), group mean deslorelin plasma levels were 155.8, 572.1 and 944.1 pg/ml in the 1X, 3X and 5X dose groups, respectively. After the second implantation (day 189), deslorelin plasma levels increased drastically in a proportional manner to up to 671.4, 2590.6, and 3535.9 pg/ml in the 1X, 3X and 5X groups, respectively, after which levels remained relatively stable up to day 210 in all treated groups. Six months after the second implantation (day 363), deslorelin plasma levels were reduced back to levels comparable to ones observed six months after the first implantation. After the third implantation (day 371), deslorelin plasma levels increased drastically in a proportional manner up to levels comparable to the ones observed after the second implantation.

The applicant concludes that, under the conditions of this study, subcutaneous administration of deslorelin acetate (4.7 mg) extended-release (6 months) implants administered to dogs at 1X, 3X and 5X the recommended dose was effective in suppressing fertility in both intact male and female dogs. No systemic adverse concerns for safety were observed in animals treated up to five times the intended therapeutic dose, except for treatment-related local reactions observed at the injection sites and the expected atrophy and hypoplasia of the male and female reproductive organs as well as impeded reproductive function.

The applicant's conclusion on the efficacy of the IVP is supported.

The field study was designed as a multi-centre, randomised, blinded and negative controlled field trial at thirteen veterinary clinics in France and Spain. 83 client-owned intact pre-pubertal female dogs were enrolled in the study of both pure breed or crossbreed, aged between 12 and 18 weeks (inclusive at inclusion). The dogs were randomised in a 3:1 ratio, 62 in IVP group and 21 in control product (CP) group.

On day 0 deslorelin acetate 4.7 mg was dosed by implant, which was injected subcutaneously in the back between the lower neck and the lumbar area by a pre-loaded implanter. The reference item in the negative control product was physiological saline (1 ml of 0.9% saline, s.c.).

The investigator performed a general physical examination, an ultrasound examination of female reproductive system and assessed heat signs on day 0, day 7, day 21, 3 months, 6 months and thereafter every second month until study completion. In addition, the investigator collected a blood sample for analysis of clinical pathology and hormonal parameters and a vaginal cytology sample that was assessed for oestrus signs by a pathologist at a contract research organisation. The owner also assessed heat signs and adverse reaction between scheduled visits, and, at presence of heat signs, an unscheduled visit at the veterinary practise was arranged.

After day 21 visit, a dog completed the study once it was confirmed to be sexually mature by the laboratory results or if it reached month 30 visit being still pre-pubertal. Three dogs were withdrawn from the study, because they were sexually mature before day 21 post implantation (aged 17 to 18 weeks).

For safety purposes, adverse events (AEs), serious adverse events and human adverse events were recorded. No hormonal treatment used for reproductive purposes was allowed and other concomitant treatments were allowed and recorded. One dog in the IVP group was excluded from the efficacy analysis, because it accidentally ingested the owner's hormone treatment.

Dogs in the IVP group reached sexual maturity significantly later than dogs in the control product (CP) group ($p<0.0001$). This was reflected by the median time to sexual maturity, which was prolonged by 160 days in the IVP group, when compared to CP. The magnitude of delay seemed to increase at the later timepoints, which was reflected by some dogs becoming sexual mature almost two years after treatment with the IVP. There were no parameters predicting an extended duration of the effect by analysing the last quartile of efficacy duration in both the IVP and CP group, involving fourteen and six dogs respectively.

Oestradiol and progesterone concentrations at sexual maturity were similar between treatment groups. At month 6 and 7 visits there were significantly more dogs presenting signs of heat in the CP group (18.8% and 16.7%) than in the IVP group (0% at both visits). There was no statistically significant difference between the groups at any of the other timepoints. The comparison of how many animals showed clinical signs of heat during the study should be used with caution, because most of the signs of heat occurred during unscheduled visits (when the owner observed signs of oestrus between scheduled visits), why animals which had clinical signs of heat in between the scheduled visits were not included in the analysis. This gives a misleading high number of animals without clinical signs at some of the timepoints. Furthermore, only one of the clinical signs was needed, and restlessness and frequent urination could easily have other aetiologies than pro-oestrus or oestrus. The most common observed signs of heat were vulvar swelling, bloody vaginal discharge, immobility reflex, restlessness, frequent urination, and attraction of males. Clinical signs of heat were detected in almost all animals of both groups (98.2% and 100% in the IVP and CP groups, respectively) at the time sexual maturity was confirmed by laboratory results. None of the dogs reached the 30-month timepoint, since all reached sexual maturity (as determined by laboratory findings) before month 30 visit. The descriptive analysis of the concordance between laboratory results and clinical signs of heat showed that no clinical signs to declare a female dog on heat were necessarily present when the animal was confirmed to be sexually mature by the laboratory results. Similarly, although some heat signs were identified (10.4% and 21.4% in IVP and CP group, respectively), the animal was not confirmed to be sexually mature by the laboratory results.

Thirty-one (50%) dogs in the IVP group experienced 104 adverse events and six (28.6%) dogs experience 17 adverse events in the CP group. The analysis of severity revealed that 89 out of 104 AEs (85.58%) in the IVP group were classified as "mild" or "moderate" in nature and 14.42% as severe or life threatening compared with all AEs classified as "mild" or "moderate" in the CP

group. There are six reported events in five dogs all having received the IVP, which all involve dermatitis or eczema. All adverse events concerning dermatitis/eczema have been assessed with causality N-unlikely. These adverse events occurred in two cases 3-4 weeks after implantation with the IVP, and in the other four cases it occurred after 25-30 weeks. As the IVP is an implant continuously releasing active substance the time from implantation to potential adverse events is not necessarily predictable. This adverse reaction is mentioned in section 4.6 (Adverse reactions) of the product information.

Eleven "life threatening" AEs (from two dogs) clearly had no relation to treatment of the IVP. Most (15 out of 16) of the AEs assessed "probable" were related to the three dogs withdrawn from the study before day 21, because of early sexual maturity.

A follow up survey of dogs included in the field study was performed, where the applicant followed the female dogs for up to 24 months after the signs of their first oestrus. Seventy-three (73) dogs that had completed the field study (IVP:52, CP: 21) were enrolled in the follow-up survey.

Initially, 83 female dogs (IVP:62 and CP:21) were included in the field study. Among the 62 dogs in the IVP group, two animals died during the field study (run over by car and parvovirus), four animals were withdrawn from the per protocol population of the field study (three displayed signs of heat before day 21 and one ate owner's contraceptive pill) and four were lost of follow-up before providing any data, which lead to 52 animals in the IVP group of the follow up study.

A form was filled out by the investigator every six months after end of the field study for up to 24 months. Descriptive reproductive data was collected concerning the time between signs of oestrus, mating/insemination, pregnancies, abortions, oestrus related pathologies, and spaying.

The first oestrus observed in all the dogs occurred during the field study, while time to the following heats after first heat was analysed in the follow up study. The applicant did not include all data for observing second, third, fourth, and fifth heat, because not all data was relevant for comparison.

The mean time between first and second heat was 6.7 months in both groups, and between second and third it was 7.6 months for IVP group and 5.9 months for CP group. Four animals of each group reached fourth heat with mean time between third and fourth heat of 6.2 months for IVP group and 6.6 months for CP group. The fifth heat was only observed in one animal from the IVP group (1.9%), 7.2 months after the fourth heat and in two animals (9.5%) from the CP group at 6.5 and 7.0 months after their fourth heat.

All observed mating in the survey led to a pregnancy in both groups. No abortions were observed in either of the groups. No malformed puppies were recorded in either of the groups.

Only one pregnancy was reported in the CP group, six months after its sexual maturity. In the IVP group, a total of nine pregnancies were reported, three on the first heat and six during following heats. Two of the dogs had two pregnancies, where the first pregnancy for both dogs went well with respectively five and seven puppies. In the following pregnancy for those two dogs, one died during labour and the other one was spayed at one-month pregnancy to avoid the term. The last dog being pregnant on the first heat gave birth to nine alive puppies and one stillborn puppy. Out of the last four dogs being pregnant in following heats, one gave birth to six puppies, one was inseminated and mated, and gave birth to a single puppy, and one was spayed at one-month pregnancy to avoid the term. The last one did not show visible signs of heat leading to pregnancy (had two previous heats with signs), and the delivery had to be assisted with a caesarean section and lead to birth of six alive puppies. Summing-up, in the IVP group six pregnancies in five bitches

were completed with one to nine alive puppies.

One animal in the IVP group was reported by the owner to have had prolonged oestrus for 24 days. Two animals (3.6%) in the IVP group suffered from pseudopregnancy signs (galactorrhea) respectively at 5.5 and 2.5 months after the first heat and one animal in the CP group (4.8%) at 3.5 months after the first heat. Follicular resorption was observed in one animal in the IVP group, where a live foetus of normal size and some embryonic vesicles with remains of placenta and embryonic material was observed by ultrasound scan at five weeks of pregnancy. Another ultrasound scan was performed one week later, and the foetus was still alive, but the remains of embryonic vesicles had disappeared. One alive puppy was born. No other reproduction related pathologies were observed during the data collecting period of 24 months after first oestrus in any of the treatment groups.

The applicant concludes on the field study and the follow up study that the IVP significantly delayed the onset of oestrus following its administration by a median of 160 days. Once sexual maturity was reached, clinical signs of heat and hormonal levels did not differ between groups, confirming that after being treated with the IVP, the female dogs becoming sexually mature are displaying normal heat signs. However, the IVP triggered heats: 3 (4.84%) female dogs out of the 62 that received the implant presented heat signs within 21 days of being treated with the IVP. This could be explained by unexpected early sexual maturity. These animals were 16 and 17 weeks old at implantation. For sexually immature female dogs, the administration of the IVP was safe in terms of severity and frequency when compared with the negative control group. The IVP did not show any long-term negative impacts on the reproductive function of female dogs; therefore, the IVP can be used safely in female dogs intended for breeding.

The applicant's conclusions on the efficacy of the IVP are supported. No difference after occurrence of the first oestrus between frequency and regularity of oestrus between the two treatment groups was noted. There are no differences in the incidence of heat related pathologies after the occurrence of the first oestrus after treatment with the veterinary medicinal product compared to the placebo treated animals.

There is no indication of altered pregnancy course after treatment with the IVP, though the number of female dogs being pregnant in the period of data collection was sparse. Considering the importance of the limited amount of data, for owners who wish to use the female dog in breeding post treatment, the available data is reflected in the product information, section 4.5.

2.2.2. New target animal species - cats

The proposed indication for the new target animal species cats is "For the induction of temporary infertility and suppression of urine odour and of sexual behaviours such as libido, vocalisation, urine marking, and aggressiveness in intact male cats from 3 months of age". In support of the above indication, the applicant provided the results of a pharmacokinetic/pharmacodynamic study, one target animal safety, and one clinical field study together with a documentation of the plasma profile of the active substance deslorelin acetate from the same field study.

The **pharmacokinetic (PK)/ pharmacodynamic (PD) properties** of the IVP were studied in a non-GLP study in 3-month-old male cats: 10 cats (plus 3 extra during the first two weeks) implanted with the IVP in the interscapular region and 5 control cats. Regarding PKs, very high deslorelin concentrations were seen 2 hours after administration of the implants, reflecting a considerable burst release. Already at the 24-hour time-point, these high concentrations abruptly decreased (by 85-98%) – a decrease corresponding to that seen after approximately 3-5 half-lives,

indirectly showing that deslorelin has a very short elimination half-life as typically seen with small peptide hormones. An implication of the short half-life is that the plasma deslorelin concentrations measured dynamically reflect the drug release rates from the implanted depots. Starting on day 2, the plasma concentrations generally slowly decreased and at the end of the study (after 71 weeks), deslorelin plasma concentrations were still measurable in 5/10 treated cats with concentrations ranging from 6-75 pg/ml. The other 5 cats had non-measurable deslorelin concentrations (< 4 pg/ml) at earlier timepoints, starting after 52 weeks for one treated cat, i.e. one calendar year after implantation (when the mean plasma concentration was 54 ± 38 pg/ml for the other 9 treated cats). A large variation was seen in the plasma deslorelin concentrations (likely reflecting variation in drug release), and the individual PK curves showed that cats with a large drug release initially also were those that first showed levels below the lower limit of quantification (LLOQ). Conversely, the two cats with the lowest drug release initially had the highest plasma exposures at the end of the study. The PD matched the PK in the study. Thus, the first cats to show signs of puberty were the ones that first had unmeasurable deslorelin concentrations and conversely, the two cats with highest concentrations at the end of the study did not show signs of puberty. The plasma testosterone concentrations were the most sensitive in terms of identifying reversal; the andrological effects of increased testicular size and penile spines followed 3-4 months later. The effect of the IVP on sexual and reproductive behaviours was less clear in this study, and the study was too short to show the full reversal to normal reproductive physiology in all cats. At study end – after 16.5 calendar months – only 5 of 10 male cats had fully reverted. No serious adverse events were seen and the only noticeable adverse event was injection site reactions; with crusts and wounds related to the large needle size, and tumefactions in 5/13 treated cats 7 days after implantation (which resolved within 7 days).

The **target animal safety (TAS) study** was a GLP-compliant study performed in cats that were slightly under 3 months of age at first dosing. Three groups of cats, each allocated 4 males and 4 females, were dosed subcutaneously with 0X, 1X and 3X the proposed dose (interscapularly and laterally on both hindlimbs) three consecutive times at six months intervals and euthanised four weeks after the last dosing (on day 393). The cats were carefully followed clinically, with special focus on the injection sites, and with several blood samplings performed for the assessment of standard haematology and biochemistry parameters as well as for measurement of deslorelin exposure. At euthanasia, a full gross pathological examination and sampling for histological analysis was performed. In brief, the only noticeable findings in the study were that the cats treated with the implants showed local effects at the implantation sites (especially the interscapular site), a marked suppression of the development of the reproductive organs and an open femur physis. The fact that all male cats were pre-pubertal (and had descended testicles at first dosing) precludes conclusions regarding potential initial increases in sexual behaviour (related to the burst release of deslorelin) and side effects on testicular descendance. The testicular atrophy was quite marked and as reversibility was not evaluated in this study, it is not known whether the suppression associated with prolonged treatment of pre-pubertal male cats will be fully reversible. The local reactions were generally mild and reversible, but, at study end, three male cats showed severe swelling (i.e. > 4 cm in diameter) at the interscapular injection site, with two appearing 10 and 13 days after the last dosing and one persisting since the second dosing (i.e. for more than 7 months). In female cats, which were also included in the TAS study, swellings at the interscapular injection site were also common, but none were severe. Also, no local reactions were observed by either owners or veterinarians in a follow-up study in which 22 male cats from the pivotal field study received a second Suprelorin implant and were followed for 12 months. This is surprising, seeing that the lowest grade for swelling was defined as ≤ 5 mm in that study and that the TAS study showed markedly more swelling both in terms of frequency and severity. The recording of mild swelling can plausibly be different between studies, but this cannot account for differences

regarding more marked swellings. Still, the data from the follow-up study show that the second implantation does not result in more marked local reactions than the first implantation. This is also supported by a couple of surveys. The delayed closure of the growth plate is a well-known effect of the product and it was therefore not monitored during the in-life phase of the study (in accordance with the scientific advice from 2018). In conclusion, the study showed that high and repeated doses of deslorelin administered to pre-pubertal cats caused local effects at the implantation sites, especially the intrascapular implantation site, and, in addition, caused a marked decrease in size of the reproductive organs as well as preventing the closure of growth lines in the long bones. While the safety regarding repeated applications per se was addressed, the safety of prolonged and repeated use with full (yearly) treatment intervals was not investigated.

The **pivotal field trial** was a multicentre, double-blinded, GCP-compliant study, including 154 Suprelorin treated (IVP) and 51 control cats (ITT and safety population). The included cats were all intact, healthy, male, indoor, aged 12 weeks or older (mean 1.5 year; range 3 months to 11 years) with normal genital appearance. On day 0, the cats were treated subcutaneously in the interscapular region with either the IVP or 1.0 ml saline. At the visits at the veterinary clinic (at screening and after approximately 1.5, 3, 6, 9 and 12 months), the cats were examined clinically, with extra focus on the injection sites and the genitals, and blood/urine was sampled. The owners were contacted by telephone by the veterinarian at study day 7 and at 1, 2, 4, 5, 7, 8, 10 and 11 months after dosing with focus on injection site, general health, concomitant treatments, appetite, and male sexual behaviour / signs. The primary efficacy criterion was serum testosterone level $\leq$ 0.10 ng/ml, and secondary efficacy criteria were penile spines, mean testicular volume, and a sexual behaviour sum score based on the following parameters: vocalisation, urine marking, aggression, and urine odour. The PP population only consisted of 128 animals: 117 in the IVP and 11 in the control group – as many cats dropped out of the study, most (56.9% of the controls and 2.6% of the IVP-treated cats) due to unwanted signs of male reproductive behaviour. Regarding the primary efficacy criterion (serum testosterone level $\leq$ 0.10 ng/ml), the IVP-treated cats showed significantly higher success rates than the controls at all time points (1.5 to 12 months after treatment; $p < 0.001$ for each time point). The sexual behaviour score was significantly lower in the IVP group than in the controls at all time points (all $p < 0.001$). The IVP group also showed a significantly higher decrease from baseline than the controls for the single sexual behaviour scores: from day 7±1 onwards regarding vocalisation and from day 31±3 onwards for the remaining parameters. Finally, the IVP group at each post-baseline visit from the 1.5-month time point onwards showed significantly less penile spines than the control cats and had smaller testicles. Evaluations based on the per protocol population gave similar results. Regarding safety, at least one local reaction at the implantation site (redness, pain or heat) was observed by the owners in 5 animals (3.25%) in the IVP group (difference 0.0325 (CI [0.0045;0.0605]), and by the veterinarian in 9 (5.84%) animals in the IVP group and in one control animal (1.96%) (difference 0.0388 (CI [-0.0143;0.0919]). Swelling (≤ 5 mm) at the implantation site was observed in 4 (2.6%) animals in the IVP group and in one animal (2.0%) in the control group at Day 0 and at Day 45±3 in 3 (2.03%) animals in the IVP group only. Swellings > 5mm were never observed. No clinically relevant differences were observed for rectal temperature. Compared to baseline, the mean body weight increased by 0.75 kg in the IVP group and by 0.35 kg in the control cats at study end (P=0.0003). The applicant has discussed the risk that the product increases the risk of body weight increase and has provided a suitable description of that risk in the product information. At most timepoints, little difference was found between the two groups regarding appetite, but at one of the timepoints (3 months after treatment), a higher increase in appetite was found in the IVP group than in the controls. Abnormal testicular evaluation results were observed at a very low level (1 animal at 1.5 and 3 months after treatment described as "very soft"). The percentage of adverse events was similar in both groups ($p = 0.85$), as well as the

incidence of serious adverse events (p = 0.77) and of adverse events suspected to be product related (p = 0.58). No relevant post baseline abnormalities of haematology, blood biochemistry or urinalysis parameters were observed. Regarding PK, the IVP group showed a slow and continuous decline in mean deslorelin values from 676 pg/ml ± 460.8 (mean ± SD), 336 pg/ml ± 227.8, 125 pg/ml ± 119.8 and 48 pg/ml ± 77.5 after the first, second, third and fourth trimester, respectively. At the same time points, the number of cats with deslorelin concentrations below the LLOQ (4 pg/ml) increased (4/139 (3%); 5/136 (4%); 5/47 (11%); 22/64 (34%). At study end, the concentrations were still quantifiable for 42 of the 64 cats (66%) for which a blood sample was collected.

In the follow-up study, 22 cats in the IVP group were re-implanted and 12 control cats were given saline at 12 months and followed for an additional 12-month period. The primary efficacy parameter was successful suppression of testosterone to levels below 0.10 ng/mL. The ratio of success was 100% at clinic visits 1.5 months post-implantation(p-i), 3 months p-i and 6 months p-i, 93.3% at 9 months p-i, and 87.5% at 12 months p-i, which is similar to the success rates obtained after the first implant. Other efficacy and safety results in the group that received a second implant were also very consistent with the results obtained in the first study. Specifically, no local reactions were observed by either owners or veterinarians.

Reversibility has been assessed in several published studies. In mature cats, a total of 24 male cats (15 implanted with the 4.7 mg dose and 9 with the 9.4 mg dose) all showed reversibility – in the former group after approximately 2 years on average (up to 32 months) (Goericke-Pesch et al., 2014; Gültiken et al., 2017; Favre et al., 2018; Romagnoli et al., 2019). In addition, two studies showed reversibility in a total of 30 male mature cats when the implants were removed after 3-4 months (n=18), 6 months (n=6), and 9 months (n=6), (Novotny et al., 2012; Ferré-Dolcet et al., 2020). In one of the studies, fertile matings (resulting in normal litter sizes) were documented 7-42 weeks after the last time point where testosterone levels were found to be below 0.1 ng/ml (Goericke-Pesch et al., 2014). In pre-pubertal male cats, the literature is sparse. In one study, 8 male cats were implanted with a third of the standard dose (1.6 mg) within the first 24 hours after birth (Carranza et al., 2014). The puberty was markedly delayed (42-91 weeks) and when – after puberty – the cats mated with female cats in oestrous, two of eight treated male cats were found not to be fertile. The PK study performed by the applicant was too short to show full reversibility in approximately half of the treated cats. The applicant has discussed evidence of reversibility in male cats and provided additional data from the follow-up study, in which 12 cats were followed for an additional 12-month period. In all 12 cats, the suppression of the testosterone level stopped before 21 months post-implantation. No data, however, were generated relative to full reversal to a fertile state. The applicant has provided information in the SPC accordingly, specifying that careful consideration should be given to using the product in male cats that might be used for breeding afterwards, and that cases of infertility have been reported following prolonged exposure due to overdoses in both kittens and mature cats.

3. Benefit-risk assessment of the proposed change

Suprelorin is authorised for the induction of temporary infertility in healthy, entire, sexually mature male dogs and ferrets. The product is presented as implant with different strengths, containing 4.7 mg or 9.4 mg deslorelin (as deslorelin acetate), a synthetic gonadotrophin-releasing hormone (GnRH) analogue.

The proposed grouped variation only concerns the implant containing 4.7 mg deslorelin and is to add the following:

a) a new therapeutic indication: "For the induction of temporary infertility to delay the first oestrus and heat signs, and to prevent pregnancy at young age in intact and healthy sexually immature female dogs" and

b) a new non-food producing target species, cats, with the following indication: "For the induction of temporary infertility and suppression of urine odour and of sexual behaviours such as libido, vocalisation, urine marking, and aggressiveness in intact male cats from 3 months of age".

The GnRH agonist 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, intact or surgically neutered, to synthesise and/or release follicle stimulating hormone (FSH) and luteinising hormone (LH), the hormones responsible for the maintenance of fertility as well as secondary sexual behaviours.

3.1. Benefit assessment

Direct therapeutic benefit

The therapeutic benefits of the two variations were supported by a clinical study for each of the species. In addition, a PK/PD study was presented for male cats, and PK data were presented from the field study for female dogs.

For the new therapeutic indication in female dogs, the product was demonstrated to induce temporary infertility indicated by a delay of the first oestrus and signs of heat by approximately 160 days (median) when administered to prepubertal animals aged between 12 and 16 weeks at inclusion. The expected benefit hereof is to prevent a too early pregnancy at young age in intact and healthy sexually immature female dogs.

In male cats, Suprelorin was shown to induce temporary infertility in sexually immature or mature intact male cats, as demonstrated by a significantly reduced serum testosterone levels ($\leq$0.10 ng/mL) at 3, 6, 9 and 12 months after treatment when applied to cats between 3 months and 12 years of age. The sexual behaviour score (vocalisation, urine marking, aggression, and urine odour) was significantly lower in the IVP group than in the controls at all time points (all $p < 0.001$).

Neutering of male cats is often necessary to prevent the animal from unintended mating and/or showing unwanted behaviour. Surgical castration of male cats is an irreversible procedure that carries a risk of surgical and/or anaesthetic complications. The main benefits of Suprelorin in male cats is that it involves a much simpler procedure (likely carrying less risk of serious complications), and that it can provide a temporary effect.

3.2. Risk assessment

Quality:

Quality remains unaffected by this variation.

Safety:

Risks for the target animal:

Administration of deslorelin acetate in accordance with SPC recommendations is generally well tolerated. The potential for mild and transient adverse local effects such as swelling, scabbing and lumps at the injection site cannot be excluded.

The effect on sexual behaviour from the initial burst release has not been fully documented in male cats as the respective TAS study was performed in pre-pubertal cats.

Concerns have been raised with regard to the long-term effects of deslorelin and reversibility of its effects:

- Potential delayed entry of sexual maturity was observed after treatment both for female dogs and male cats.
- Increased body weight gain was observed in male cats.
- Reversion to fertility has not been sufficiently determined in male cats. There may be a risk of male cats not returning to a fully fertile state after cessation of the action of Suprelorin.
- Repeated administration in female dogs was not supported by data. Therefore, the indication for female dogs can only be considered valid for single use of the IVP, which is clearly stated in the product information.

The identified risks are addressed in the product information.

Risk for the user:

The risk for the user (professional veterinarians) remains unaltered by this variation.

Risk for the environment:

Suprelorin is not expected to pose a risk for the environment when used according to the SPC recommendations. No new concerns for the environment are foreseen to arise from this variation.

Special risks:

No special risks have been identified.

3.3. Risk management or mitigation measures

Information has been included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal and to provide advice on how to prevent or reduce these risks.

Additional SPC text has been included to address concerns raised in regard to target animal safety, including to warn against repeated use in female dogs and to state the risk of reduced fertility in male cats.

3.4. Evaluation of the benefit-risk balance

No change to the impact of the product is envisaged on the following aspects: quality, user safety, and environmental safety.

The benefits of Suprelorin in female dogs is a delay of the first oestrus and heat signs, and to prevent pregnancy at a young age. The benefit of Suprelorin in male cats is induction of temporary infertility and suppression of urine odour and of sexual behaviours such as libido, vocalisation, urine marking, and aggressiveness in sexually immature or mature intact male cats from 3 months of age.

For both species it is considered that the risks are adequately reflected in the SPC and that the benefit-risk balance is positive.

4. Conclusion

Based on the original and complementary data presented on safety and efficacy, the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Suprelorin can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008), as follows:

Addition of a new therapeutic indication: "For the induction of temporary infertility to delay the first oestrus and heat signs, and to prevent pregnancy at young age in intact and healthy sexually immature female dogs" and

Addition of new non-food producing target species, cats, with the following indication: "For the induction of temporary infertility and suppression of urine odour and of sexual behaviours such as libido, vocalisation, urine marking, and aggressiveness in intact male cats from 3 months of age"

Changes are required in the following Annexes to the Community marketing authorisation:

I, IIIA and IIIB

Please refer to the separate product information showing the tracked changes.

As a consequence of these variations, sections 1, 4 and 5 of the SPC are updated. The corresponding sections of the Package Leaflet are updated accordingly.