ACC&D
Alliance for Contraception in CATS & DOGS

SUPRELORIN®

September 2020

Product Profile and Position Paper (4P)

Suprelorin® is a subcutaneous implant containing the active ingredient deslorelin acetate. Originally developed in Australia, it is currently marketed by Virbac and approved for sale in approximately 40 countries. It is indicated "for the induction of temporary infertility in healthy, entire, sexually mature male dogs." It is manufactured in two versions, which induce infertility for a minimum of 6 months (4.7 mg) or 12 months (9.4 mg).

The active ingredient, deslorelin, is a gonadotropin-releasing hormone (GnRH) agonist that causes infertility by down-regulating pituitary receptors for GnRH, suppressing gonadotropins as well as testosterone. The implant has also been studied or used "off-label" for contraception of female dogs, cats of both sexes, and wildlife species in captivity.

Suprelorin®

CONTRACEPTIVE IMPLANT FOR MALE DOGS CONTRACEPTIVE IMPLANT FOR MALE DOGS

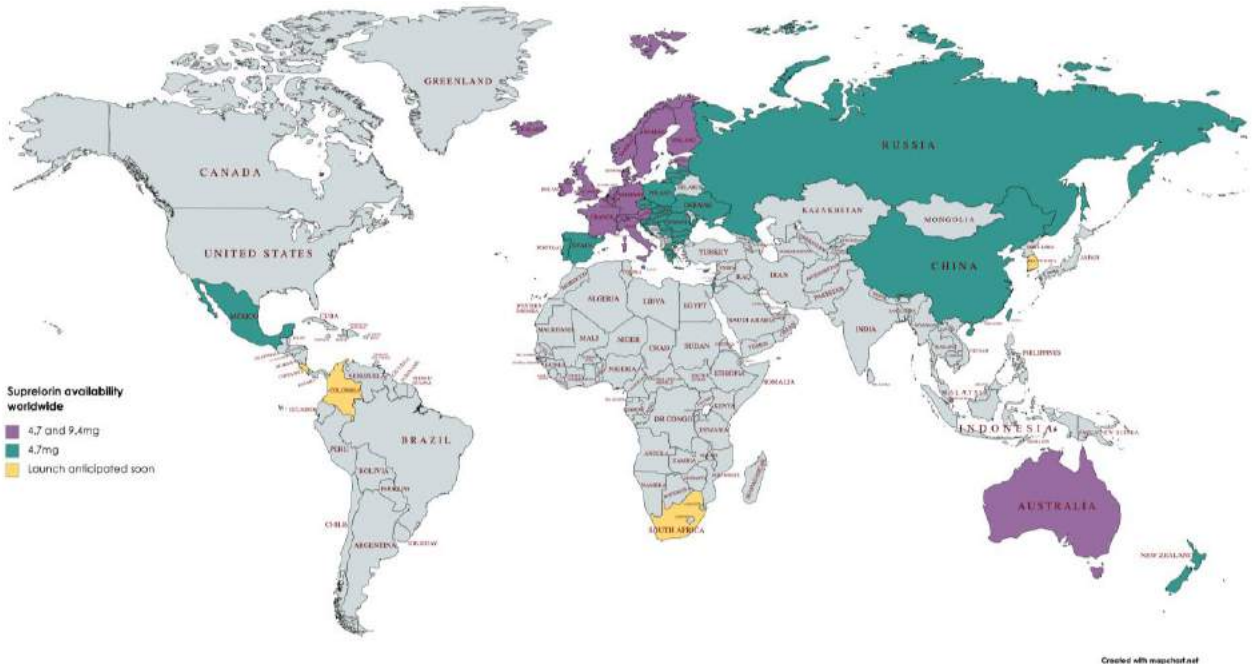
INTRODUCTION

Suprelorin® is a subcutaneous implant that contains the active ingredient deslorelin acetate. It is indicated for suppression of fertility for 6–12 months in male dogs, depending on the dosage used. The product has been studied in male and female dogs and cats of both sexes to understand safety, efficacy, and duration. There are also some data on its use to control fertility of wildlife species in captivity.

This paper presents a profile of Suprelorin, describing the product and its approved use in male dogs, including data on its safety and effectiveness for this approved use. Key literature describing Suprelorin's use off label in female dogs and in other species is reviewed. In addition, this paper summarizes the risks and benefits of Suprelorin and ACC&D's position on use of the drug both "on label"—that is, for temporary infertility in male dogs—and "off label" in female dogs and cats of both sexes. ACC&D does not promote or advocate off-label use of this product, but we provide this information as a resource for interested stakeholders.

PRODUCT PROFILE

Suprelorin is a subcutaneous implant containing deslorelin, a gonadotrophin releasing hormone (GnRH) agonist drug. It is available on the order of a veterinarian. The drug is formulated in a small implant designed to remain underneath the skin. The implant comes pre-packaged in a single-dose sterile syringe and needle. There are two versions, containing either 4.7 or 9.4 mg of deslorelin, that are designed to suppress fertility in male dogs for a minimum of 6 or 12 months, respectively. The implant is inserted in the general area of the back of the neck and can be repeatedly dosed to extend the period of suppression of fertility. As of September 2020, Suprelorin is available in approximately 40 countries worldwide (see map for details).



MECHANISM OF ACTION

Deslorelin, the active ingredient in Suprelorin, is a gonadotropin-releasing hormone (GnRH) agonist. Deslorelin is a small peptide that has activity similar to GnRH, the body's master reproductive hormone. GnRH is released in pulses by the brain. This pulsatile release is critical for normal reproduction, as GnRH is bound by receptors on the pituitary gland, causing the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH). In the case of the deslorelin implant, the drug is released slowly and continuously at low doses over time, and this pattern of release suppresses, rather than stimulates, fertility. This prolonged and continuous stimulation of pituitary GnRH receptors by deslorelin leads to desensitization of these receptors, which in turn suppresses production of LH and FSH, which ultimately results in a suppression of testosterone in males and estrogen and progesterone in females (Fontaine & Fontbonne 2011).

However, it is important to point out that before this suppression, the initial exposure to deslorelin acts on the pituitary to increase LH and FSH secreted into the bloodstream. This initial stimulation occurs until the GnRH receptors on the pituitary are down-regulated, which can be over a period of 5-10 days. In males this will cause an initial increase in testosterone, followed by suppression, and in females, depending on when in the estrus cycle she is dosed, may induce an estrus, followed by a suppression of estrus.

In male dogs, suppression of testosterone caused by deslorelin suppresses fertility by stopping sperm production, decreasing seminal fluid, and, in some dogs, reducing libido and sexual behaviors. The prostate gland will also decrease in size, similar to the effects seen from surgical castration. In females, fertility is suppressed by inhibiting ovulation.

MALE DOGS

The only indication for which Suprelorin has regulatory approval is the use in male dogs. A small survey of veterinarians showed that Suprelorin is used in male dogs for a variety of reasons (Driancourt and Briggs 2020). In order of frequency:

- When surgery is a risk (age/risk of anesthesia)
- To provide reversible suppression of fertility in breeding males (i.e., to make them infertile for a short period)
- When owners are reluctant to castrate
- As a "test-run" before surgical castration (e.g., when an owner would like to permanently sterilize their dog through surgery but would like to "try out" what suppression of testosterone will do to their dog's personality and behavior)
- When male and female dogs are living in the same household for a temporary period
- To manage inappropriate behavior
- When owners want to avoid any risk of reproduction
- To treat benign prostatic hyperplasia (BPH)
- To treat perianal gland tumors

EFFECTIVENESS

Suprelorin has been demonstrated to be effective in the suppression of fertility in male dogs. As mentioned above, dogs can receive additional implants for continued contraception. It is important to note in all scenarios that a male dog treated with Suprelorin for the first time is not immediately infertile and should be assumed to remain fertile for at least 6-8 weeks after treatment. Although fertility is likely to return if a dog is not re-implanted, the time to return to fertility is extremely variable and can be very long in some cases. Therefore, the label does not indicate the time to reversibility of this treatment, but rather the minimum time that a dog will remain infertile based on the studies conducted for regulatory approval.

Below is a summary of the data submitted to the European Medicines Agency (EMA) for approval of Suprelorin (EMA 2012).

Suprelorin was evaluated in client-owned male dogs weighing 10–25 kg (22–55 lbs). Fertility was evaluated by measuring plasma testosterone levels, and treated dogs had testosterone levels similar to those seen in surgically castrated dogs. Dogs also had reduced testicle size, decreased libido, and decreased spermatogenesis (sperm produced in the testicles). In most dogs (>95%) these effects started at about 6 weeks after implantation. Note that in a separate study, under laboratory conditions, infertility was achieved 5–14 weeks after initial treatment.

In the study of client-owned dogs, over 80% of dogs receiving one or more 4.7mg implants returned to normal testosterone levels within 12 months, and 98% within 18 months. However, data demonstrating the reversibility of clinical effects (including fertility) after 6 months, or after repeated implantation, are limited. In rare cases, even one implantation can cause the temporary infertility to last more than 18 months. A dog's weight does not affect the recommended implant dosage or treatment schedule, but most of the smaller dogs (<22 lbs) maintained suppressed testosterone for more than 12 months following implantation.

In clinical trials of dogs who received one 9.4 mg implant, 68% returned to normal testosterone levels within 2 years of implantation, and 95% within 2.5 years. As with the 4.7mg implant, data demonstrating the reversibility of clinical effects after 12 months, or after repeated implantation, are limited.

In clinical studies, the majority of dogs treated with either the 4.7 or the 9.4 mg implant regained normal semen approximately one year after the last treatment, and dogs have been able to mate successfully with bitches after treatment with Suprelorin was stopped.

Other studies have also shown reversibility of infertility and confirmed large variability in the time from implantation to return to fertility with both implant sizes (Junaidi et al. 2003, 2009). Virbac (2016) reports that trials with up to four consecutive implants have demonstrated that treated dogs can return to fertility after treatment ends, although timing is variable.

SAFETY

Multiple studies have found Suprelorin to be safe and well tolerated (Lucas 2014). The implant may cause moderate swelling at the implantation site in the two weeks after treatment, and/or local reactions (e.g., inflammation, hardening) for up to 3 months; these resolve naturally (EMA 2012).

The safety of Suprelorin has been studied after giving laboratory dogs more than 10 times the recommended dose, with no side effects observed. The label recommends the implants not be used in prepuberal dogs, as its use in this age group has not been investigated.

OFF-LABEL USE

Researchers and veterinarians have investigated the use of Suprelorin in young male dogs, and in animals of other species and ages. Below is a review of some of the literature related to "off-label" uses in female dogs and cats of both sexes. It is important to note that the extensive efficacy and safety studies required for regulatory approval that were completed in male dogs have not been performed for other sexes or species. Driancourt and Briggs (2020) offer an extensive review of the literature related to use of deslorelin in male dogs. Additional information about off-label use in female dogs and cats is also available in ACC&D's *Contraception and Fertility Control in Dogs and Cats* (section 3.2.1.1).

Suprelorin® for male ferrets

Suprelorin (9.4 mg) has been approved in the EU and Australia for contraception in intact sexually mature male ferrets (hobs). While treated ferrets may remain infertile up to 4 years, mating more than 16 months after treatment may result in pregnancy (EMA 2012).

FEMALE DOGS

Adult and juvenile female dogs have been treated with Suprelorin in laboratory studies, in clinical studies of client-owned dogs, and in field studies with free-roaming dogs.

Female dogs have long periods of anestrus and come into estrus (heat) at variable times, making evaluation of long-term infertility challenging. For example, for female breeds with an average inter-estrous interval of 9–12 months, clinical trials would need to be conducted for up to two years to demonstrate fertility suppression.

As in male dogs, deslorelin can cause initial stimulation of the pituitary. Depending on the stage of estrus of the bitch, Suprelorin can induce a fertile estrus (within approximately two weeks of implantation) that is then followed by suppression of fertility (Romagnoli et al. 2009, Fontaine et al. 2011, Fontaine & Fontbonne 2012, von Heimendahl & Miller 2012, Lucas 2014). If a bitch has high levels of serum progesterone, then treatment with Suprelorin does not induce an estrus (Trigg et al. 2001).

Methods to prevent the estrus induced by Suprelorin treatment have been explored. Some investigators have used treatment with progestins prior to Suprelorin implantation, but results of progestin use have been inconsistent (Sung et al. 2006, Fontaine & Fontbonne 2012). In the field study conducted by Dogs With No Names, described below, the investigators sought to compensate for induced estrus by targeting lactating and prepubescent dogs for treatment; they have not reported induced estrus, although the study was not designed to observe for or detect estrus.

There have been no large studies of Suprelorin in bitches to determine the duration of fertility suppression. A study in 10 bitches concluded that the 4.7 mg implant may suppress estrus if administered at 4.5-month intervals; a 9.4 mg implant was used in four of these animals and inhibited estrus for 11–14 months (Romagnoli et al. 2009).

Suprelorin has been used in free-roaming female dogs in an attempt to decrease the number of unwanted puppies in the community. A field study conducted in Canada by Dogs With No Names (DWNN) administered the 9.4 mg implant to free-roaming female dogs in Canada's First Nations communities. In one study, DWNN targeted lactating and prepubescent (4–6 months of age) females but treated dogs aged 3 months to 8 years.

What is Suprelorin® F?

Superlorin® F is a U.S. Food & Drug Administration (FDA) Indexed Product to manage adrenal gland disease in sterilized and sexually intact male and female ferrets. It is available as a 4.7mg dose. It is not FDA approved, but rather legally marketed as an FDA Indexed Product (FDA 2012). This is a rare designation for veterinary drugs. Extra-label use of Suprelorin F is prohibited and grounds for removal from the market.

Ninety-six dogs were initially implanted; 44 were re-implanted at 12-to-24-month intervals.[1] No bitch became pregnant within the 2 months following her first implant, and no re-implanted bitch gave birth. One female produced a litter after 9 months, indicating poor response to or failure of the implant (Samson-French & Rogers 2013).

Formal safety studies in female dogs have not been published. Side effects have not been reported in female dogs in various published studies, but these studies were not designed to detect abnormalities or side effects (Romagnoli et al. 2009, Samson-French & Rogers 2013). In a study of 80 client-owned female dogs who received a 4.7 mg implant, Palm and Reichler (2010) observed 11 (13.8%) of the dogs, all of which were older (mean age ~5 years), develop metropathy (uterine disease), leading the authors to advise against use of Suprelorin in older females, as well as those previously treated with progestins. Metropathy was not observed in younger female dogs.

Data on safety in pregnant or lactating dogs are limited. In some field studies of free-roaming dogs, female dogs may be trapped and implanted without knowing their reproductive status, and may be pregnant or lactating when treated in a population control effort.

In the DWNN study described above, 6 of 96 (6.25%) dogs were unknowingly pregnant when implanted; they produced normal litters and were not observed to return into heat in the next 12–24 months. Fourteen females received implants while lactating. This did not appear to compromise lactation or health of nursing puppies, and bitches were not observed in heat for at least 12 months (Samson-French & Rogers 2013). Data on survival of pups born to bitches treated while pregnant are only anecdotal.

PRE-PUBERTAL DOGS

Use of deslorelin has been studied in pre-pubertal dogs of both sexes and shown to delay puberty (see, e.g., Sirivaidyapong et al. 2012, Marino et al. 2014, Kaya et al. 2015). The safety of Suprelorin in younger dogs has not been studied.

CATS

Suprelorin has the same mechanism of action in cats as in dogs. There is an initial stimulation of testosterone in males, and an induced estrus in females, followed by suppression of testosterone in males, and inhibition of estrus in females, causing infertility.

Extensive studies on safety and effectiveness have not been conducted in cats, but a number of small studies have explored effects in this species. A review of the scientific literature is given in the ACC&D publication Contraception in Dogs and Cats (section 3.2.1.1, 2013). Below is a summary.

ADULT MALE CATS

Data in male cats are based on a limited number of small studies with 4.7mg implants. Studies have used plasma testosterone, testosterone-related physical features (penile spines, testicular volume), and behavior (urine marking, libido, mounting, and mating), as well as limited breeding trials, to evaluate fertility and implant efficacy.

[1] A portion of treated dogs died or disappeared during the study and thus could not be monitored. Deaths and disappearances are attributed to the harsh living conditions in the region.

Studies have demonstrated a transient stimulation phase (increase in testosterone) in adult tomcats in the 1–2 weeks after Suprelorin treatment. As in dogs, male cats will likely be fertile for a limited period after treatment. Goericke-Pesch et al. (2011) found that the majority of treated cats exhibited an increase in sexual behavior (libido, mounting, mating) lasting approximately 2 weeks. After this stimulation, these behaviors subsided such that cats showed physical and behavioral characteristics similar to those expected of a surgically sterilized male.

Studies in a small number of male cats (<10) treated with a 4.7 mg implant have found variability in the time to suppression of fertility, as measured by testosterone levels and associated physical characteristics (Goericke-Pesch et al. 2011, Novotny et al. 2012, Fontaine 2015). One study observed that within about 3 weeks of treatment, 50% of cats had basal testosterone levels; within 11 weeks, this increased to 90% had basal testosterone levels (Goericke-Pesch et al. 2011). Testosterone-dependent penile spines disappeared after approximately 9 weeks, on average (Goericke-Pesch et al. 2011).

In another study, testosterone and spermatogenesis data suggest sperm counts significantly decreased 4 months after treatment, but complete azoospermia (absence of viable sperm) took longer to achieve (Novotny et al. 2012, 2015). Data suggest that it may take 2–3 months following treatment for a cat to become infertile, but diminished libido at 2 months might limit desire to breed (Novotny et al. 2012).

One long-term study found variability in the duration of efficacy in adult male cats (n=7); a 4.7 mg implant suppressed fertility for, on average, approximately 19 months (range: 15–25 months) (Goericke-Pesch et al. 2014).

Research on the effects of Suprelorin treatment on subsequent fertility in male cats is limited, and sample sizes are very small. Goericke-Pesch et al. (2014) measured fertility following long-term treatment with one 4.7 mg implant; duration of efficacy varied between 61.7 and 100.7 weeks (mean 78.8 ± 12.9 weeks). As the effects of the treatment wore off, and testosterone levels increased, development of penile spines and increase in testis size were observed. The interval from the first measurable testosterone increase and impregnation ranged from 7–42 weeks (attributed at least in part to seasonality). Novotny et al. (2012) removed a 4.7 mg implant after 4 months and evaluated return to fertility. They observed incremental increase in testosterone levels and progressive reestablishment of spermatogenesis as early as 1 month after removal. Within 4 months, testosterone levels, sperm count, and testis size returned to pretreatment levels. Because of the correlation between the increase in testosterone and physical changes, evaluation of the testes size and penile spines can be useful in assessing continued efficacy of the implant without measuring serum testosterone.

Tomcats have tolerated Suprelorin well. Although studies have not been designed to evaluate safety, treated cats have shown no local reactions (e.g., swelling or scratching), and clinical exams and blood counts and serum biochemistry values have not indicated any specific safety issue (Fontaine 2015).

ADULT FEMALE CATS

Concentrations of progesterone and estradiol, monitoring of estrus behaviors, and pregnancy are means by which Suprelorin efficacy and return to fertility have been measured in adult female cats.

After treatment with Suprelorin, it is common for female cats to experience an induced estrus. Studies demonstrate that individual variability influences this induced estrus, as does the time in the cycle during which a queen is implanted (Lucas 2014). Studies also suggest that sex hormone levels often do not correspond with behavioral estrus (Munson et al. 2001, Toydemir et al. 2012, Goericke-Pesch et al. 2013a, Zambelli et al.

2015). It is likely that the estrus induced by treatment is fertile, although there are limited data to support this (Toydemir et al. 2012; Zambelli et al. 2015).

Megestrol acetate, a progestational drug, has been used to prevent induced estrus by administering it orally for two weeks before and after Suprelorin implantation. This approach is common in zoo cats, with good results in preventing an induced estrus (personal communication, Dr. Cheryl Asa, May 11, 2016). Data in queens are very limited. Toydemir et al. (2012) treated queens (n=7) with 9.4 mg deslorelin and megesterol acetate (5 mg at 14 days and 12 hours before, and 14 days after, Suprelorin treatment) and found that although an estradiol increase was seen during and immediately after deslorelin treatment in 6 of 7 queens, no queens exhibited behavioral signs of estrus, and fecal estradiol levels were reduced one day after deslorelin treatment.

There is significant variability in the duration of efficacy of Suprelorin implants in queens. A 4.7 mg Suprelorin implant suppressed fertility in 20 treated queens for between 16 and >37 months (Goericke-Pesch et al. 2013a). The 9.4 mg implant administered to 21 queens was found to suppress estradiol secretion and estrus behavior for 18.5 months in most queens, at which point cats were spayed (Toydemir et al. 2012). No data exist on maximum duration of contraception.

One study suggests that Suprelorin's suppression of fertility in female cats is reversible after long-term treatment. Goericke-Pesch et al. (2013a) found that eight female cats were mated during their first known estrus that occurred after suppression of fertility caused by implantation of the 4.7 mg implant; seven cats became pregnant immediately, and the eighth shortly after; all queens delivered successfully.

Suprelorin has been tolerated well in studies to date, although studies have not been designed to evaluate safety. Minimal and temporary swelling at the insertion site has been observed in some female cats in the few days immediately after treatment. General health, blood counts/serum biochemistry, and social behavior have all been assessed in queens and no obvious abnormalities were seen following treatment with Suprelorin (Munson et al. 2001, Fontaine 2015).

Safety data in pregnant cats treated with Suprelorin are very limited and only anecdotal. A case report of a queen mated in error approximately one week before receiving a 4.7mg implant notes that although the queen delivered four healthy kittens, she showed no interest in them and had inadequate lactation (Goericke-Pesch 2013b). In some cases this inability to lactate adequately after Suprelorin treatment has been observed in captive wildlife as well (personal communication, Dr. Cheryl Asa, May 11, 2016).

PRE-PUBERTAL CATS

Deslorelin has been studied in neonatal and pre-pubertal cats of both sexes and shown to delay puberty (see, e.g., Risso et al. 2012, Carranza et al. 2014). The safety of deslorelin in kittens has not been studied.

ACC&D POSITION

Suprelorin represents an important tool to suppress fertility in male dogs. It is the first GnRH agonist to be approved and commercialized for this indication. It provides a safe and effective means to suppress fertility in male dogs for 6-12 months.

Things to consider when contemplating using Suprelorin in male dogs include:

- The drug is a prescription drug and available only through veterinarians.
- It is simple to use, requiring only a subcutaneous implantation with no anesthesia.

- After implantation, a male dog may continue to be fertile for up to 6–8 weeks, and should be kept away from bitches in estrus to prevent breeding.
- Although the drug is likely reversible, the length of time to regaining fertility is variable and may be long. If dogs are re-implanted over multiple years, there may be a chance that fertility suppression will be permanent.
- Because fertility suppression is maintained by periodic re-implantation, in situations where long-term suppression is desired, dogs will need to be available for follow up re-implantation. This may be difficult in feral or community dogs without a single owner.
- The effects on behavior have not been well studied. However, because Suprelorin reduces testosterone to limits below the level of detection it can be assumed that it will have impacts on behavior similar to castration for the duration of efficacy.
- Suprelorin is unlikely to offer significant value for population control of free-roaming/community male dogs, as reproductive capability of females has significantly more impact on population numbers. As such, the product offers more value for use by owners of pet dogs, or by breeders.

Things to consider when contemplating using Suprelorin off label:

ACC&D does not advocate for off-label use of Suprelorin, but in situations where its use is considered, the following should be taken into account:

- Female dogs
  - The long-term efficacy and safety in female dogs has not been well studied.
  - In female dogs, treatment may induce a fertile estrus, resulting in unwanted pregnancy unless the female is kept from fertile males.
  - The effect of treating a pregnant bitch, including the potential effects on her puppies, has not been well studied.
- Cats
  - The long-term efficacy and safety in male and female cats has not been evaluated.
  - After implantation in females, depending on the state of their estrus cycle, a fertile estrus may be induced.
  - In male cats, as in male dogs, it is likely that suppression of fertility will occur several weeks post-treatment.
  - The duration of the fertility suppression effect of Suprelorin in male or female cats is unknown, and likely to be highly variable. Sequential implants will likely be required for long-term fertility suppression.
  - The time period post-implantation to regaining fertility is not known.
- Pre-pubertal dogs and cats
  - Treatment with Suprelorin very early in life in both kittens and puppies will delay puberty but not prevent sexual maturity.

In deciding whether or not Suprelorin is the appropriate tool for fertility suppression, whether in owned animals, feral or community animals, or other applications, the risks and benefits outlined above need to be carefully considered. In some settings it can be a valuable tool for fertility suppression as an alternative to surgical castration.

REFERENCES

Alliance for Contraception in Cats & Dogs (ACC&D). *Contraception and Fertility Control in Dogs and Cats.* 2013. Available at http://www.acc-d.org/docs/default-source/Resource-Library-Docs/accd-e-book.pdf.

Carranza A, Faya M, Lopez Merlo M, Batista P, Gobello C. Effect of GnRH analogs in postnatal domestic cats. *Theriogenology* 2014;82(1):138-143.

Driancourt M-A, Briggs J. Gonadotropin-releasing hormone (GnRH) agonist implants for male dog fertility suppression: a review of mode of action, efficacy, safety, and uses. *Front Vet Sci*. 2020;7.

European Medicines Agency (EMA). *EPAR summary for the public: Suprelorin (Deslorelin).* 2012. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/veterinary/000109/WC500068830.pdf.

Fontaine C. Long-term contraception in a small implant: A review of Suprelorin (deslorelin) studies in cats. *Journal of Feline Medicine and Surgery*. 2015;17:766–71.

Fontaine E, Fontbonne A. Clinical use of GnRH agonists in canine and feline species. *Reprod Dom Anim*. 2011. 46: 344–53.

Fontaine E, Mir F, Vannier F, Gerardin A, Albouy M, Navarro C, Fontbonne A. Induction of fertile oestrus in the bitch using Deslorelin, a GnRH agonist. *Theriogenology* 2011;76:1561–66.

Goericke-Pesch S, Georgiev P, Antonov A, Albouy M, Wehrend A. Clinical efficacy of GnRH-agonist implant containing 4.7-mg deslorelin, Suprelorin, regarding suppression of reproductive function in tomcats. *Theriogenology* 2011;75:803–10.

Goericke-Pesch S, Georgiev P, Antonov A, Vodenicharov A, Navarro C, Wehrend A. Reversibility of germinative and endocrine testicular function after long-term contraception with a GnRH agonist implant in the tom—a follow-up study. *Theriogenology* 2014;81:941–6.

Goericke-Pesch S, Georgiev P, Atanasov A, Albouy M, Navarro C, Wehrend A. Treatment of queens in estrus and after estrus with a GnRH-agonist implant containing 4.7 mg deslorelin; hormonal response, duration of efficacy, and reversibility. *Theriogenology* 2013a;79:640–6.

Goericke-Pesch S, Georgiev P, Atanasov A, Wehrend A. Treatment with Suprelorin in a pregnant cat. *J Feline Med Surg*. 2013b;15(4):357–60.

Junaidi A, Williamson PE, Cummins JM, Martin GB, Blackberry MA, Trigg TE. Use of a new drug delivery formulation of the gonadotrophin-releasing hormone analogue Deslorelin for reversible long-term contraception in male dogs. *Reprod Fertil Dev*. 2003;15(6):317–22.

Junaidi A, Williamson PE, Martin GB, Blackberry MA, Cummins JM, Trigg TE. Dose-response studies for pituitary and testicular function in male dogs treated with the GnRH superagonist, Deslorelin. *Reprod Domest Anim*. 2009;44(5):725–34.

Kaya D, Schäfer-Somi S, Kurt B, Kuru M, Kaya S, Kaçar C, Aksoy Ö, Aslan S. Clinical use of deslorelin implants for the long-term contraception in prepubertal bitches: effects on epiphyseal closure, body development, and time to puberty. *Theriogenology*. 2015;83(7):1147–53.

Lucas X. Clinical use of Deslorelin (GnRH agonist) in companion animals: a review. *Reprod Dom Anim*. 2014;49 (Suppl. 4): 64–71.

Marino G, Rizzo S, Quartuccio M, Macrì, Pagano G, Taormina A, Cristarella S, Zanghì A. Deslorelin implants in pre-pubertal female dogs: short- and long-term effects on the genital tract. *Reproduction in Domestic Animals*. 2014;49(2):297–301.

Massei G, Miller LA. Nonsurgical fertility control for managing free-roaming dog populations: A review of products and criteria for field applications. *Theriogenology* 2013;80:829–38.

Munson L, Bauman JE, Asa CS, Jöchle W, Trigg TE. Efficacy of the GnRH analogue deslorelin for suppression of oestrous cycles in cats. *Journal of Reproduction and Fertility Supplement*. 2001;57:269–73.

Novotny R, Cizek P, Vitasek R, Bartoskova A, Prinosilova P, Janosovska M. Reversible suppression of sexual activity in tomcats with deslorelin implant. *Theriogenology* 2012;78:848–857.

Palm J, Reichler IM. Effectiveness of deslorelin acetate for the suppression of heat in the bitch. 7th EVSSAR Congress; May 14–15, 2010; Louvain-La-Neuve, Belgium.

Risso A, Corrada Y, Barbeito C, Diaz JD, Gobello C. Long-term release GnRH agonists postpone puberty in domestic cats. Reprod Domest Anim 2012; 47: 936–938.

Romagnoli S, Stelletta C, Milani C, Gelli D, Falomo ME, Mollo A. Clinical use of deslorelin for the control of reproduction in the bitch. *Reprod Dom Anim*. 2009;44(Suppl 2):36–9.

Samson-French J, Rogers L. The use of contraceptive implants (Suprelorin) to control unwanted dog populations on First Nations reserves – a retrospective study. 5th International Symposium on Non-Surgical Contraceptive Methods of Pet Population Control; June 20-22, 2013; Portland, Oregon. http://www.acc-d.org/docs/default-source/5th-symposium/samson-french_deslorelin_abstract.pdf. Accessed April 13, 2016.

Sirivaidyapong S, Mehl NS, Trigg TE. Delay of puberty and reproductive performance in male dogs following the implantation of 4.7 and 9.4 mg GnRH-Agonist Deslorelin at an early pre-pubertal age. 7th International Symposium on Canine and Feline Reproduction; July 26-29, 2012; Whistler, Canada. http://www.ivis.org/proceedings/iscfr/2012/148.pdf?LA=1 (accessed May 26, 2016).

Sung M, Armour AF, Wright PJ. The influence of exogenous progestin on the occurrence of proestrous or estrous signs, plasma concentrations of luteinizing hormone and estradiol in deslorelin (GnRH agonist) treated anestrous bitches. *Theriogenology*. 2006;66(6–7):1513–17.

Toydemir TSF, Kilicarslan MR, Olgaç V. Effects of the GnRH analogue deslorelin implants on reproduction in female domestic cats. *Theriogenology* 2012;77:662–74.

Trigg TE, Wright PJ, Armour AF, Williamson PE, Junaidi A, Martin GB, et al. Use of a GnRH analogue implant to produce reversible longterm suppression of reproductive function in male and female domestic dogs. *J Reprod Fertil Suppl* 2001;57:255–61.

Von Heimendahl A, Miller C. Clinical evaluation of Deslorelin to induce oestrus, ovulation and pregnancy in the Bitch. *Reprod Dom Anim*. 2012;47(Suppl 6):398–99.

Virbac. 2016. Suprelorin brochure. https://www.virbac.com.au/files/live/sites/au-public/files/pdf/dog-cat/Non-surgical-castration.pdf.

Walter B, Otzdorff C, Brugger N, Braun J. Estrus induction in beagle bitches with the GnRH-agonist implant containing 4.7mg deslorelin. *Theriogenology*. 2011;75(6):1125–29.

Zambelli D, Bini C, Küster DG, Molari V, Cunto M. First deliveries after estrus induction using deslorelin and endoscopic transcervical insemination in the queen. *Theriogenology*. 2015;84:773–78.