**SUPRELORIN® (DESLORELIN) GnRH AGONIST IMPLANTS FOR CONTRACEPTION:**

**RESEARCH INVESTIGATION**

# Agreement of Participation

The AZA Reproductive Management Center (RMC) is sponsoring a basic research study of the efficacy of the gonadotropin-releasing hormone (GnRH) agonist deslorelin in implant form (Suprelorin®). The Center, as part of an agreement with Virbac, Australia, will supply implants to participating AZA-accredited institutions. The RMC will also work with AZA Sustainability Partners to supply implants for animals that are part of an SSP managed population. The product is approved for sale in the U.S. only for treating ferret adrenal disease, and any other use must be for research only. Thus, all participating institutions must agree to submit annual reports to the RMC with information regarding product use. A signed request for an implant will be considered agreement to participate in the research program. Annual terms of participation include:

1) Signed Agreement of Participation

2) Updating animal records on the AZA Reproductive Management Center’s contraception database [website](http://www.zoocontraceptiondata.org/)

3) Submission of reproductive tracts and adverse reaction forms to Dr. Dalen Agnew, Reproductive Health Surveillance Program

**Product Information**

Deslorelin achieves contraception by temporarily suppressing the reproductive endocrine system, preventing production of pituitary (FSH and LH) and gonadal hormones (estradiol and progesterone in females and testosterone in males). The observed effects are similar to those following ovariectomy or castration, but are reversed after the hormone content of the implant is depleted or the implant is removed and the animal’s reproductive system has had time to recover. As a hormone agonist, deslorelin first stimulates the reproductive system, which can result in estrus and ovulation in females or temporary enhancement of testosterone and semen production in males. Then down-regulation follows the initial period of stimulation. Deslorelin has been effective in females of a wide range of species, but not in male ungulates or marsupials tested to date. Efficacy in females can be monitored by estrous behavior or gonadal steroids in feces. Efficacy in male dogs has correlated well with testosterone suppression, but documentation of absence of sperm may be important in other species. Even after spermatogenesis is interrupted, there may be viable sperm in the ejaculate for weeks or possibly even months, as is the case following vasectomy.

Trials to date have focused primarily on domestic dogs (Trigg et al. 2001), although there has been one controlled study in domestic cats (Munson et al, 2001) and preliminary data from a number of exotic species (Bertschinger et al. 2001 and 2002). These investigations have not detected any adverse effects, although weight gain was common, as is often the case following castration or ovariectomy. In all cases where reversibility was tested, reproductive function was fully restored. Recent results from tests of another GnRH agonist with prepubertal domestic cats found that estrous cycles occurred after treatment ended. GnRH agonists should not be used during pregnancy, but may be safe to use during lactation, only after milk production is fully established.

Suprelorin implants are available in two formulations: minimum 6-month (4.7mg) and minimum 12-month (9.4mg) implants. Time to reversal is extremely variable and likely depends on a number of factors, including the animal’s age, the consecutive number of treatments, whether implants were removed, and individual differences in ability to recover physiologically from suppression. Data from various species have shown, though, that individual responses tend to be consistent, that is, an animal reverses at 8 months if likely to reverse at 8 months following subsequent treatment. If you cannot wait for signs of reversal to determine duration of efficacy, then for continuous contraception the 4.7-mg implants should be replaced at least every 6 months and the 9.4-mg implants at least every 12 months. Although implants become more porous and friable over time, removal is possible and is recommended to hasten time to reversal. Proper insertion can facilitate later removal (see instructions supplied with implant or on the RMC webpage: [www.stlzoo.org/contraception](http://www.stlzoo.org/contraception) under Product/Suprelorin).

The RMC determines the proper dose for each request based on reports of successful use for each species.

**References**

Bertschinger, H.J., Asa, C.S., Calle, P.P., Long, J.A., Bauman, K., DeMatteo, K., Jöchle, W., Trigg, T.E., and Human, A. (2001) Control of reproduction and sex related behaviour in exotic wild carnivores with the GnRH analogue deslorelin. J. Reprod. Fert., Suppl. 57: 275-283.

Bertschinger, H. J., Trigg, T. E., Jöchle, W., and Human, A. (2002) Induction of contraception in some African wild carnivores by downregulation of LH & FSH secretion using the GnRH analogue deslorelin. Reproduction, Suppl. 60: 41-52.

Munson, L., Bauman, J.E., Asa, C.S., Jöchle, W., and Trigg, T.E. (2001) Efficacy of the GnRH-analogue deslorelin for suppression of the oestrous cycle in cats. J. Reprod. Fert., Suppl. 57: 269-273.

Trigg, T.E., Wright, P.J., Armour, A.F., Williamson, P.E., Junaidi, A., Martin, G.B., Doyle, A.G., and Walsh, J. (2001) Use of a GnRH analogue implant to produce reversible long-term suppression of reproductive function in male and female domestic dogs. J. Reprod. Fert., Suppl. 57: 255-261.

**PARTICIPANT INFORMATION**

**Project: Investigation of the Efficacy of Suprelorin® (deslorelin) Implants for Contraception**

**Sponsor: AZA Reproductive Management Center at the Saint Louis Zoo**

 **for Virbac, Australia**

**Sponsor Contact Information:**

 Ashley Franklin

 Saint Louis Zoo

 1 Government Drive

 St. Louis, MO 63110

 314-646-4732; fax: -5534

 franklin@stlzoo.org

**Product Information:**

 Active ingredient: Deslorelin (GnRH agonist)

 Inactive ingredients: various lipids

Dosages: 4.7mg in minimum 6-month matrix or 9.4 mg in minimum 12-month matrix for SQ placement

 (insertion device included); Dosages are assigned by the Reproductive Management Center

 Manufacturer/Source: Virbac, AUS

Costs: $35 per 6-month (4.7mg) implant; $65 per 12-month (9.4mg) implant, to be paid to the Reproductive Management Center as reimbursement, at cost (product is not for commercial sale)

**(Please complete the following)**

**Date**:

**Collaborating Institution:**

**Institution D&B D-U-N-S Number:**

**Contact person:** (person responsible for data collection and reporting)

Name:

Mailing address:

Phone/Fax/e-mail address:

**Animal Information:**

Species (genus/species and common name):

Name, Local ID, GAN, and studbook numbers for each individual:

Birth Date(s):

Gender(s):

Body Weight(s):

Date of most recent birth (offspring) for males and females:

Name and email address for the Manager or Curator for this animal:

For non-mammals: explain the reason for this implant request. Please be specific, detailing any past and current medical problems related to the reproductive tract.

**Product Duration of Efficacy Requested** (6-month or 12-month):

**\*Suprelorin is made available by Virbac Australia only for use in the species and number of individuals designated in this agreement.**

**AGREEMENT OF PARTICIPATION**

I, the undersigned, understand that this request is being initiated for an investigational product, Suprelorin® (deslorelin) contraceptive implant, that has not been extensively tested in non-domestic species. As a participant in this study, I will provide information on efficacy and any deleterious effects, including updating this/these animal(s) records on the AZA Reproductive Management Center contraception database website at <http://www.zoocontraceptiondata.org/>.

Signed\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_(Attending or Chief Veterinarian)

Printed\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_(Attending or Chief Veterinarian)

**The AZA Reproductive Management Center is required to submit contact information for the Veterinarian signing this document to FDA. Please fill out the following information:**

**Title:**

 **Email address:**

**Phone Number:**

**Please indicate if you are employed full-time or part-time by the Zoo or Institution where the animal is housed, or if you are a contracted or consulting veterinarian:**

**If contracted or consulting, please provide the name, address and phone number for your primary place of business:**

**DESLORELIN (SUPRELORIN®) CONTRACEPTIVE STUDY**

**INSTRUCTIONS FOR PARTICIPANTS**

**Material Testing Agreement:**

Deslorelin (Suprelorin®) is made available by Virbac Australia to the AZA Reproductive Management Center for research only in designated species. The RMC must make results of the research available to Virbac. (See instructions for Reporting below)

**Implant Insertion:**

The implant comes sterilized and pre-loaded in an insertion device. The recommended site of implant placement was originally between the shoulder blades. That site is still appropriate if removal will not be needed, but because removal is desirable in most cases, the RMC has developed alternative locations for implant placement that facilitate later removal. The ideal site will vary by species, but examples of those that have been successful have been SQ ventral to the ear, inner area of the leg (front or rear), and the inguinal area. Although the animal may be able to lick or scratch these areas, deep placement of the implant at the end of a tunnel created by the trocar can protect it. An instructional video illustrating implant placement SQ in the inner aspect of the rear leg can be seen on the AAZV and AZVT websites.

The area should be clipped and cleaned using standard surgical prep techniques. A fold of skin should be lifted and held between the thumb and fingers, as the obturator (supplied with the implant) is inserted. To prevent implant breakage during insertion, create a tunnel with the trocar, then slowly withdraw the obturator, leaving the implant in place in the tunnel. The implant should be held steady as the obturator is removed to ensure release of the implant so that it remains in place under the skin.

**Latency to Effectiveness:**

Because the initial effect is to stimulate the reproductive system, it is important to either separate treated animals from opposite sex individuals during the period of enhanced fertility or use another form of contraception. Females treated with deslorelin should be considered fertile for 3 weeks following insertion. Males may remain fertile for 2 or more months, until residual sperm either degenerate or are passed (as following vasectomy).

**Use of Ovaban to Suppress Initial Estrus/Ovulation:**

The estrus and ovulation that can occur within 2 weeks following implant insertion can be suppressed with supplemental progestin treatment for 15 days (7 days before and 8 days following implant insertion) (Wright et al. 2001). Megestrol acetate (not melengestrol acetate: MGA) available as Ovaban® in tablet form is the simplest method for short-term progestin administration. The tablet can be offered in a treat to ensure ingestion. The dose of Ovaban®, which comes in 5- and 20-mg tablets, for domestic dogs is 2mg/kg body weight (veterinarians can obtain Ovaban®). Dose must be extrapolated for other taxa.

If the animal has an unexpired MGA implant in place (i.e., less than 2 years), MGA removal could be delayed until 3 weeks after deslorelin implant insertion.

**Monitoring Behavior:**

Please record any signs of estrous behavior, male sexual interest, mounting or copulation. Reproductive behavior should be completely suppressed after the initial period of stimulation. Reappearance of sexual activity is a sign that deslorelin levels may be below the threshold of efficacy and that fertility is not suppressed. In deslorelin-treated males, suppression of testosterone should be accompanied by decreased sexual interest and aggression.

**Reporting:**

All participants are required to report immediately any adverse effects that might be related to the use of deslorelin implants to Ashley Franklin at the RMC (314-646-4732, Franklin@stlzoo.org). In addition, participants are required to update animal records on the AZA Reproductive Management Center contraception database website at <http://www.zoocontraceptiondata.org/>. Contact Ashley Franklin for website registration, a user’s manual, or if you have any questions or technical issues while using the website (314-646-4732, Franklin@stlzoo.org).

**Health Surveillance Monitoring**

In collaboration with the Reproductive Health Surveillance Program, the RMC conducts pathology surveillance to identify adverse reactions that might be associated with contraceptive products. We are requesting reproductive tracts from all male and female mammals treated with contraceptives, as well as from *non-contracepted individuals,* so we can compare normal changes with lesions arising from contraceptive use*.* Contact Dr. Dalen Agnew, Michigan State University, at 517-353-1683, agnewd@dcpah.msu.edu or Dr. Anneke Moresco, Anneke\_moresco@hotmail.com

**Fecal Hormone Monitoring**

For those institutions wishing to monitor suppression via fecal gonadal hormones, arrangements can be made with Dr. Corinne Kozlowski, Endocrinologist for the RMC, at 314-646-4762 or kozlowski@stlzoo.org.

**Reference**

Wright, P.J., Verstegen, J.P., Onclin, K., Jochle, W., Armour, A.F., Martin, G.B., and Trigg, T.E. (2001) Suppression of the oestrous responses of bitches to GnRH analogue deslorelin by progestin. J. Reprod. Fert., Suppl. 57: 263-268.

 **APPENDIX I:**

**COLLECTION, STORAGE AND SHIPMENT OF FECAL SAMPLES**

1. Collect sample as fresh as possible.

2. Scoop up about a spoonful (inexpensive plastic coffee spoons are convenient for this).

3. Place in small zip-lock bag. Do not overfill bag, and make sure it is well sealed.

4. Frequency of collection will vary by species, please contact endocrinologist for recommendation.

5. Using permanent black marker (Sharpie) on white opaque marking area on bag, clearly label with Species, Animal ID, and Date of collection.

6. Freeze immediately. Store at -70°C if possible, but a regular freezer (-20°C) is acceptable for short-term storage (30-60 days).

7. Ship on dry ice by overnight courier to:

 Corinne Kozlowski, Ph.D.

 Research Department

 Saint Louis Zoo

 1 Government Drive

 St. Louis MO 63110

8. Mark box “Frozen Specimens”. Include information in the box clearly identifying species, Deslorelin Study, and contact information for the sender.

9. Before shipping, notify Dr. Corinne Kozlowski (314-646-4762 or kozlowski@stlzoo.org) to expect the package.

10. Costs: $17 per hormone assayed; if 20+ samples are sent at a time the cost is $15 per hormone.