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FREEDOM OF INFORMATION SUMMARY

ORIGINAL REQUEST FOR ADDITION TO THE INDEX OF LEGALLY MARKETED UNAPPROVED NEW ANIMAL DRUGS FOR MINOR SPECIES

MIF 900-013

SUPRELORIN F
Deslorelin acetate
Domestic Ferrets

“For the management of adrenal gland cortical disease in the male and female domestic ferret”

Requested by:
Virbac AH, Inc.
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I. GENERAL INFORMATION:

A. File Number: MIF 900-013

B. Requestor: Virbac AH, Inc.
3200 Meacham Boulevard
Fort Worth, Texas 76137

Drug Labeler Code: 051311

C. Proprietary Name(s): SUPRELORIN F

D. Established Name(s): Deslorelin acetate

E. Pharmacological Category: Hormone

F. Dosage Form(s): Subcutaneous implant

G. Amount of Active Ingredient(s): 4.7 mg of deslorelin (as acetate) per implant

H. How Supplied: Implant is supplied in a sterile implanting needle with an unattached non-sterile multi-use actuator syringe.

I. How Dispensed: By veterinary prescription (Rx)

J. Dosage(s): 1 implant (4.7 mg of the active ingredient) every 12 months

K. Route(s) of Administration: Injection (subcutaneous implantation)

L. Species/Class(es): Domestic ferrets

M. Indication(s): For the management of adrenal gland cortical disease in the male and female domestic ferret

II. EFFECTIVENESS AND TARGET ANIMAL SAFETY:

In accordance with 21 CFR part 516, a qualified expert panel evaluated the target animal safety and effectiveness of the SUPRELORIN F (deslorelin acetate) 4.7 mg implant for use in the management of adrenal gland cortical disease in male and female domestic ferrets to determine whether the benefits of using SUPRELORIN F for the proposed use outweigh its risks to the target animal. The members of the qualified expert panel were:

Robert A. Wagner, VMD, Diplomat ABVP-ECM, Pittsburgh, PA;
A. FINDINGS OF THE QUALIFIED EXPERT PANEL:

Based on a review of the literature, anecdotal reports and personal use, it is the unanimous opinion of the expert panel that the benefits of using SUPRELORIN F (deslorelin acetate) 4.7 mg implants for the management of adrenal gland cortical disease in the male and female domestic ferret outweigh the risks to the target animals.

Literature references indicate the prevalence of adrenal cortical disease (ACD; also referred to as adrenal gland cortical disease in this summary) in the ferret and the risks and benefits of various treatment options. The literature also indicates that most ferrets will need to be treated for ACD during their lifetime. Simone-Freilicher indicates in a report published in 2008 that the incidence of ACD in the ferret appears to be increasing: in 1993, reports indicated that 30% of the ferret population was affected; by 2003, that number had risen to 70%. Ferrets can have one (unilateral) or both (bilateral) adrenal glands diseased. One publication reports that up to 19% of the ferrets in the study population had bilateral disease.

The clinical presentation of ACD in the ferret can be quite dramatic. The most common presenting complaints for ferrets with ACD include progressive alopecia, pruritis, enlarged vulva (with or without a mucoid discharge) in the female, dysuria or urinary blockage in the male, and sexual aggression towards other ferrets. A more severe and life-threatening sign of ACD is anemia caused by prolonged exposure to high concentrations of circulating estrogen that are toxic to the bone marrow. This anemia is seen in both male and female ferrets and although it is rare (reported in less than 15% of presenting cases of ACD), it can be life-threatening and it can alter the prognosis associated with ACD.

In the United States and many parts of the world, domesticated ferrets are desexed (spayed and neutered) at a very young age (often prior to puberty). It is believed that this early removal of the sex organs plays a role in the pathogenesis of ACD. Overall, the incidence of ACD is reported to be higher in sterilized ferrets versus those that remain sexually intact.

The use of deslorelin acetate implants in ferrets to manage adrenal gland disease was first reported in the literature in 2005. These reports indicate that use of the deslorelin acetate implant is effective in managing the clinical signs associated with adrenal gland disease. The literature reviewed by the qualified expert panel included several clinical studies in ferrets. Two are briefly summarized below.

Prohaczik and colleagues in Hungary reported on 3 cases of ACD in ferrets managed with the 4.7 mg deslorelin implant in 2009. The study tested the hypothesis that the implants could be used to manage hyperestrogenism of adrenal gland origin (referred to as ACD in this summary). Fourteen healthy ferrets were used as controls in the study. Three ferrets showing clinical signs of disease were each treated with a single subcutaneously implanted 4.7 mg deslorelin acetate implant. Plasma estradiol concentrations were measured pre-treatment and again one month after implantation in two of the three ferrets.
(the third ferret was too anemic from the disease for pre-treatment blood sampling). The two treated ferrets for which there were plasma hormone measurements, had elevated plasma estrogen concentrations pre-treatment (similar to the control ferrets in estrus) and had significantly decreased plasma estrogen concentrations (similar to the control ferrets in anestrous) one month after implantation. All three ferrets treated with the implants had resolution of the clinical signs of disease by one month post-treatment. The authors of the study concluded that the 4.7 mg deslorelin implant lowered estradiol concentrations, improved clinical symptoms in the ACD affected ferrets and provided a good option for management of ACD in the ferret.

Another reference reviewed in support of the use of deslorelin acetate implants in the management of ACD in ferrets was published by Wagner, Finkler, Fecteau, and Trigg in 2009\textsuperscript{32}. In this study, 30 pet ferrets (14 female and 16 male) with ACD were treated with 4.7 mg deslorelin acetate implants. ACD was diagnosed in the ferrets based on clinical signs and elevated hormone concentrations on the University of Tennessee Ferret Adrenal Panel. The adrenal glands of all ferrets were evaluated before treatment using abdominal ultrasound and palpation. No adverse effects from the implants were noted during this study. All ferrets had elevated concentrations of estradiol, androstenedione and/or 17-hydroxyprogesterone pre-treatment. All ferrets had clinical signs consistent with ACD, the most common of which were alopecia and vulvar swelling in the females. The report indicated an improvement in all clinical signs after treatment relative to the pre-treatment evaluation (usually within the first month post-treatment). Mean estradiol concentration for all ferrets in the study was 179.54 pmol/L pre-treatment and 130.35 pmol/L post-treatment (upper end of the reference interval for the University of Tennessee panel is 180 pmol/L). Mean plasma androstenedione concentration pre-treatment was 41.68 nmol/L and post-treatment the mean was 4.81 nmol/L (upper end of the reference interval is 15 nmol/L). Mean plasma 17-hydroxyprogesterone concentration pre-treatment was 2.27 nmol/L and post-treatment the mean was 0.24 nmol/L (the upper limit of the reference interval is 0.8 nmol/L). This study also evaluated tumor growth and found that there was no significant growth or enlargement of the adrenal glands during the treatment period. The authors stated that this suggests there is an effect (direct or indirect) of the deslorelin acetate on the control of adrenal mass and growth. Seven of the ferrets in this study were re-implanted with the 4.7 mg deslorelin acetate implant when the signs of ACD returned and these animals were successfully returned to clinical remission. This supports the use of the implant for long-term management of ACD in the ferret. The authors concluded that 4.7 mg of deslorelin acetate in an implant can safely and effectively be used in the long-term management of ACD and that hormone analysis and monitoring of clinical signs can be used to evaluate response to therapy.

The use of the SUPRELORIN\textsuperscript{®}F implant appears to be a safe treatment option as side effects reported are generally mild and self-limiting in nature (implantation site swelling and lethargy).

The expert panel also considered the risk of not having a commercially available deslorelin acetate implant for use in the ferret and determined that this could result in a lack of effective treatment, unnecessary surgical risks and off-label use of human drug products.
B. LITERATURE CONSIDERED BY THE QUALIFIED EXPERT PANEL:


III. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to SUPRELORIN F:

KEEP OUT OF REACH OF CHILDREN. Do not handle this product if you are pregnant or nursing or suspect you may be pregnant. Accidental administration may lead to a disruption of the menstrual cycle. Avoid direct skin contact with the implant; if skin contact occurs, wash the affected area immediately with soap and water. The use of gloves is advised. As with all injectable drugs causing profound physiological effects, routine precautions should be employed by practitioners when handling and using SUPRELORIN F implants to prevent accidental injection. In case of accidental human injection, a physician should be consulted and the implant should be removed.
IV. AGENCY CONCLUSIONS:

The information submitted in support of this request for SUPRELORIN F for addition to the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species (Index) for the management of adrenal gland cortical disease in the male and female domestic ferret satisfies the requirements of section 572 of the Federal Food, Drug, and Cosmetic Act (act) and 21 CFR part 516.

A. DETERMINATION OF ELIGIBILITY FOR INDEXING:

As part of the determination of eligibility for inclusion in the Index, FDA determined that the drug for this intended use in ferrets was safe to the user, did not individually or cumulatively have a significant effect on the human environment, and that the description of the methods used in, and the facilities and controls used for, the manufacture, processing and packing of the new animal drug was sufficient to demonstrate that the requestor has established appropriate specifications for the manufacture of the new animal drug. Additionally, the requestor has committed to manufacture the drug in accordance with current good manufacturing practices (cGMP).

The Index is only available for new animal drugs intended for use in minor species for which there is a reasonable certainty that the animal or edible products from the animal will not be consumed by humans or food producing animals and for new animal drugs intended for use only in a hatchery, tank, pond, or other similar contained man-made structure in an early, non-food life stage of a food-producing minor species, where safety for humans is demonstrated in accordance with the standard of section 512(d) of the act. Because this new animal drug is not intended for use in food producing animals, FDA did not require data pertaining to drug residues in food (i.e., human food safety) for granting this request for addition to the Index.

B. QUALIFIED EXPERT PANEL:

The qualified expert panel for SUPRELORIN F met the selection criteria listed in 21 CFR 516.141(b). The panel satisfactorily completed its responsibilities in accordance with 21 CFR part 516 in determining the target animal safety and effectiveness of SUPRELORIN F for subcutaneous implantation in domestic ferrets.

C. MARKETING STATUS:

In its written report, the qualified expert panel recommended that SUPRELORIN F be made available as a prescription (Rx) product for this intended use. The Agency agrees with the qualified expert panel’s recommendation that this product be restricted to use by or on the order of a licensed veterinarian.

D. EXCLUSIVITY:

Products listed in the Index do not qualify for exclusive marketing rights.
E. ATTACHMENTS:

Facsimile Labeling:

2 implant box; 5 implant box; pouch; and package insert