Date of Index Listing: June 25, 2012

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.

TABLE OF CONTENTS

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;

Karen L. Rosenthal, DVM, MS, Cayman Islands, B.W.I.; and
Mark R. Finkler, DVM, Roanoke, VA.

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[1,4,8,17,19,20,25,33]. 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%[25]. 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[1].

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[17,19]. 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[5,22]. 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[5,9].

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[2,21]. Overall, the incidence of ACD is reported to be higher in sterilized ferrets versus those that remain sexually intact[5].

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[14]. 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[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®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:

1. Besso JG, Tidwell AS, Gliatto JM. Retrospective review of the ultrasonographic features of adrenal lesions in 21 ferrets. Vet Radiol Ultrasound. 2000; 41(4):345-352.

2. Bielinska M, Kiiveri S, Parviainen H, Mannisto S, Heikinheimo M, Wilson DB. Gonadectomy-induced adrenocortical neoplasia in the domestic ferret (*Mustela putorius furo*) and laboratory mouse. Vet Pathology. 2006; 43:97-117.

3. Boari A, Papa V, Di Silverio F, Aste G, Olivero D, Rocconi F. Type 1 diabetes mellitus and hyperadrenocorticism in a ferret. Vet Res Commun. 2010; 34 (Supp 1):S107-S110.

4. Carpenter JW, Quesenberry KE. Ferrets, Rabbits and Rodents: Clinical Medicine and Surgery, 2nd ed. W B Saunders, St. Louis, 2003, pp. 83-87.

5. Chen S. Advanced diagnostic approaches and current medical management of insulinomas and adrenal cortical disease in ferrets (*Mustela putorius furo*). Vet Clin Exot Anim. 2010; 13:439-452.

6. Coleman GD, Chavez MA, Williams BH. Cystic prostatic disease associated with adrenocortical lesions in the ferret (*Mustela putorius furo*). VetPath. 1998; 35:547-549.

7. Goett SD, Degner DA. Suspected adrenocortical insufficiency subsequent to bilateral adrenalectomy in a ferret. Exotic DVM. 2003; 5:15-18.

8. Harms CA, Stoskopf MK. Outcomes of adoption of adult laboratory ferrets after gonadectomy during a veterinary student teaching exercise. Am Assoc Lab Anim Sci. 2007; 46:50-54.

9. Kawasaki T. Comments on treatment of hyperadrenocorticism in ferrets. J Am Vet Med Assoc. 2008; 233:705-708.

10. Kuijten AM, Schoemaker NJ, Voorhout G. Ultrasonographic visualization of the adrenal glands of healthy ferrets and ferrets with hyperadrenocorticism. J Am Anim Hosp Assoc. 2007; 43:78-84.

11. Lipman NS, Marini RP, Murphy JC, Zhibo Z, Fox JG. Estradiol-17ß-secreting adrenocortical tumor in a ferret. J Am Vet Med Assoc. 1993; 203:1552-1555.

12. Murray, J. Melatonin implants: An option for use in the treatment of adrenal disease in ferrets. J Exotic Mamm Med Surg. 2005; 3:1-6.

13. Paul-Murphy J, O'Brien R, Ramer J. Melatonin use in ferret adrenal gland disease. N Am Vet Conf Proc. 2001; 15:897.

14. Prohaczik A, Kulcsar M, Huszenicza G. Deslorelin treatment of hyperestrogenism in neutered ferrets (*Mustela putorius furo*): a case report. Veterinarni Medicina. 2009; 54:89-95.

15. Protain HJ, Kutzler MA, Valentine BA. Assessment of cytologic evaluation of preputial epithelial cells as a diagnostic test for detection of adrenocortical disease in castrated ferrets. Am J Vet Res. 2009; 70:619-623.

16. Ramer JC, Benson KG, Morrisey JK, O'Brien RT, Paul-Murphy J. Effects of melatonin administration on the clinical course of adrenocortical disease in domestic ferrets. J Am Vet Med Assoc. 2006; 229:1743-1748.

17. Rosenthal KL. Adrenal gland disease in ferrets. Vet Clin North Am Small Anim Pract. 1997; 27:401-417.

18. Rosenthal KL, Petersen ME. Evaluation of plasma androgen and estrogen concentrations in ferrets with hyperadrenocorticism. J Am Vet Med Assoc. 1996; 209:1097-1102.

19. Rosenthal KL, Petersen ME. Hyperadrenocorticism in the Ferret. Kirk's Current Veterinary Therapy XIII, Small Animal Practice. Philadelphia: WB Saunders Co., 2000, pp. 372-374.

20. Rosenthal KL, Peterson ME, Quesenberry KE, Hillyer EV, Beeber NL, Moroff SD, Lathrop CD. Hyperadrenocorticism associated with adrenocortical tumor or nodular hyperplasia of the adrenal gland in ferrets: 50 cases (1987-1991). J Am Vet Med Assoc. 1993; 203:271-275.

21. Schoemaker NJ, Schuurmans M, Moorman H, Lumeij JT. Correlation between age at neutering and age at onset of hyperadrenocorticism in ferrets. J Am Vet Med Assoc. 2000; 216:195-197.

22. Schoemaker NJ, Lumeij JT, Rijnberk A. Current and future alternatives to surgical neutering in ferrets to prevent hyperadrenocorticism. Veterinary Medicine. 2005; July:484-496.

23. Schoemaker NJ, Kuijten AM, Galac S. Luteinizing hormone-dependent Cushing's syndrome in a pet ferret (*Mustela putorius furo*). Dom An Endocrin. 2008; 34:278-283.

24. Schoemaker NJ, van Deijk R, Muijlaert B, Kik MJL, Kuijten AM, de Jong FH, Trigg TE, Kruitwagen CLJJ, Mol JA. Use of a gonadotropin releasing hormone agonist implant as an alternative for surgical castration in male ferrets (*Mustela putorius furo*). Theriogenology. 2008; 70(2):161-167.

25. Simone-Freilicher E. Adrenal Gland Disease in Ferrets. Vet Clin Exot Anim. 2008; 11:125-137.

26. Swiderski JK, Seim HB 3rd, MacPhail CM, Campbell TW, Johnston MS, Monnet E. Long-term outcome of domestic ferrets treated surgically for hyperadrenocorticism: 130 cases (1995-2004). J Am Vet Med Assoc. 2008; 232:1338-1343.

27. Vinke CM, van Deijk R, Houx BB, Schoemaker NJ. The effects of surgical and chemical castration on intermale aggression, sexual behaviour and play behaviour in the male ferret (*Mustela putorius furo*). J Applied Animal Behaviour Science. 2008; 115:104–121.

28. Wagner RA. Estrogen induced bone marrow depression in a ferret (*Mustela putorius furo*) with adrenal gland tumors. J Sm Exotic An Med. 1995; 3 (2):59-61.

29. Wagner RA, Bailey EM, Schneider JF, Oliver JW. Leuprolide acetate treatment of adrenocortical disease in ferrets. J Am Vet Med Assoc. 2001; 218:1272-1274.

30. Wagner RA, Dorn D P. Evaluation of serum estradiol concentrations in alopecic ferrets with adrenal gland tumors. J Am Vet Med Assoc. 1994; 205:703-707.

31. Wagner RA, Piché CA, Jöchle W, Oliver JW. Clinical and endocrine responses to treatment with deslorelin acetate implants in ferrets with adrenocortical disease. Am J Vet Res. 2005; 66:910-914.

32. Wagner RA, Finkler MR, Fecteau KA, Trigg TE. The treatment of adrenal cortical disease in ferrets with 4.7-mg deslorelin acetate implants. J Exot Pet Med. 2009; 18:146-152.

33. Weiss CA, Scott MV. Clinical aspects and surgical treatment of hyperadrenocorticism in the domestic ferret: 94 Cases (1994-1996). J Am Anim Hosp Assoc. 1997; 33:487-493.

34. Wheler CL, Kamieniecki CL. Ferret adrenal-associated endocrinopathy. Can Vet J. 1998; 39:175-176.

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