

Date of Index Listing: June 15, 2012

FREEDOM OF INFORMATION SUMMARY

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

MIF 900-012

SYNOPLEX

Poly (acetyl, arginyl) Glucosamine

Elephants and Rhinoceroses

"For topical application on animals in the family Elephantidae and Rhinocerotidae for treatment of foot and dermal lesions infected with aerobic or facultative anaerobic Gram-positive and/or Gram-negative bacteria; and for treatment of sterile chronic foot and dermal lesions"

Requested by:

Synedgen, Inc.

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I. GENERAL INFORMATION:

- A. File Number:** MIF 900-012
- B. Requestor:** Synedgen, Inc.
1420 N. Claremont Blvd., Suite 105D
Claremont, California 91711

Drug Labeler Code: 42368
- C. Proprietary Name(s):** SYNOPLEX
- D. Established Name(s):** Poly (acetyl, arginyl) glucosamine
- E. Pharmacological Category:** Anti-inflammatory/antimicrobial
- F. Dosage Form(s):** Dry soluble powder
- G. Amount of Active Ingredient(s):** Each gram of SYNOPLEX contains 1 gram of poly (acetyl, arginyl) glucosamine.
- H. How Supplied:** Synoplex® is supplied as a dry soluble powder in amber glass bottles containing 1 gram of poly (acetyl, arginyl) glucosamine, that is rehydrated with sterile water prior to use. Synoplex® is packaged in a carton containing either one (1) bottle or five (5) bottles of 1 gram of poly (acetyl, arginyl) glucosamine.
- I. How Dispensed:** By veterinary prescription (Rx)
- J. Dosage(s):** 500 µg/mL for infected wounds or 200 µg/mL for non-infected wounds in a volume sufficient to moisten the affected area
- K. Route(s) of Administration:** Topical
- L. Species/Class(es):** Elephants, rhinoceroses
- M. Indication(s):** For topical application on animals in the family Elephantidae and Rhinocerotidae for treatment of foot and dermal lesions infected with aerobic or facultative anaerobic Gram-positive and/or Gram-negative bacteria; and for treatment of sterile chronic foot and dermal lesions

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 SYNOPLEX for topical application on animals in the family Elephantidae and Rhinocerotidae for treatment of foot and dermal lesions infected with aerobic or facultative anaerobic Gram-positive and/or Gram-negative bacteria; and for treatment of sterile chronic foot and dermal lesions to determine whether the benefits of using SYNOPLEX for the proposed use outweigh its risks to the target animal. The members of the qualified expert panel were:

Charles L. Hofacre, DVM, MAM, PhD, University of Georgia;
Eric Andrew Klaphake, DVM, DACZM, DABVP, Montana Animal Medical Center; and
Ralph Zimmerman, DVM, Albuquerque Biopark.

A. FINDINGS OF THE QUALIFIED EXPERT PANEL:

Based on a thorough review of the literature and their own personal experience with this drug, the qualified expert panel concluded that SYNOPLEX is both effective and safe for topical use on animals in the family Elephantidae and Rhinocerotidae for treatment of foot and dermal lesions infected with aerobic or facultative anaerobic Gram-positive and/or Gram-negative bacteria; and for treatment of sterile chronic foot and dermal lesions.

Chitosan/poly-D-glucosamine is a naturally occurring compound found in the shells of crustaceans, such as, shrimp, lobsters and crabs. The compound Chitosan was granted an exemption from the requirements of tolerance for residues when used as a pesticide. It has been used regularly in consumer products. The EPA found there to be no residual risks to humans or to the environment "because Chitosan has not shown toxicity in mammals" (EPA Docket Number EPA-HQ-OPP-2007-0566).

Wounds in elephants and rhinoceroses are currently treated with systemic or topical antibiotics as well as topical disinfectants, such as chlorhexidine or betadine. The cost of systemic antibiotics in these large animal species can be nearly prohibitive, and systemic antibiotic use could result in multiple drug resistance in the animal's normal bacterial flora. The expert panel agrees that there is a need for a safe, simple, prophylactic and therapeutic treatment for controlling and preventing bacterial biofilms and treating both chronic and acute infections associated with dermal wounds and foot disease in elephants and rhinoceroses (West, 2001; Fowler, 2006; Mikota, 2006; Miller, 2003).

The qualified expert panel concurs with the literature that wounds or pressure ulcers of large mammals, such as elephants and rhinoceroses frequently become infected with multiple normal flora bacteria (Fowler, 2006; Mikota, 2006; Miller, 2003). These chronically infected wounds have been treated repeatedly with various antimicrobials which could result in the development of multiple drug resistant strains of bacteria. The advantage of treating these infections without use of a traditional antimicrobial product is a major benefit to the patients and to the caretakers. The cationically charged SYNOPLEX molecule, similar to chitosan, binds to the bacterial cell, resulting in the development of small pores in the bacteria's cell membrane and cell death (Tang 2010). This effect has been demonstrated *in vitro* to be effective against both gram positive and gram negative aerobic and facultative anaerobic bacteria (FDA Expert Panel Briefing).

The lack of toxicity and non-irritating effects of the product were demonstrated in the following testing: hamster mucosal pouch, chronic and acute *per os* dosing and intravenous injection in rats (FDA Expert Panel Briefing). In all studies, there were no histological, clinical chemistry or hematological adverse events.

Results of studies of the product when used in elephants and rhinoceroses demonstrated effectiveness without any adverse effects (FDA Expert Panel Briefing). One case report described the treatment of a 7000 pound female elephant that had had a chronic fistula/ulcer on the bottom of her left front #4 nail since the 1980's. The lesion was treated cryosurgically to debride the necrotic and infected tissue prior to the first 200 ppm wound rinse treatment. Wound irrigation with SYNOPLEX applied with a hand-held pump was performed daily for two months. The lesion demonstrated a slowly accumulating granulation bed with rapidly proliferating epithelium around the perimeter of the lesion. Daily debridement was no longer needed after one week. The lesion size greatly decreased and stayed cleaner during treatment. Following the daily treatments, the elephant had a smaller, milder, manageable non-infected wound that continued to be treated every 1 to 3 weeks as needed. Another case involved an elephant with a temporal gland impacted with exudate. After daily flushing with SYNOPLEX for just over one week, the lesion resolved. A third case involved a 3300 pound female rhinoceros with pressure ulcers on both hips and a deep abscess on her front left foot. After debridement, followed by 5 weeks of daily rinses with SYNOPLEX, the pressure ulcers showed excellent progress toward resolution and the foot abscess had resolved. After reviewing these and similar cases in elephants and rhinoceroses with chronic and/or acute foot and dermal lesions that were treated successfully, the qualified expert panel concluded that SYNOPLEX is safe and effective for the intended uses in the labeling and the benefits to the target animals of using the product clearly outweigh any risk to the target animals.

The expert panel also concluded there was minimal concern for the veterinarian or caretakers applying SYNOPLEX to their patients since chitosan-based products have been used as medical devices in humans (Malmquist, 2008; Wedmore, 2006). There have been no known allergic reactions or adverse events reported.

B. LITERATURE CONSIDERED BY THE QUALIFIED EXPERT PANEL:

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7. EPA Docket Number EPA-HQ-OPP-2007-0566 Chitin and chitosan: proposed registration review final decision case 6063, Biopesticides and Pollution Prevention Division.
8. FDA Expert Panel Member Review Briefing; December 11-12, 2011.
9. Fowler M. E. (2006) Chapter 20: Foot Disorders. In Fowler ME, Mikota SK. *Biology, Medicine, and Surgery of Elephants*. Blackwell Publishing. pp 271-290. ISBN-13: 978-0813806761.
10. GRAS Notification petition by Primex Ingredients (GRAS Notice No. GRN 000170) in 2005.
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III. USER SAFETY:

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

Not for use in humans. Keep out of the reach of children. In case of skin, eye contact, or ingestion, flush affected area with water. If inhalation occurs and breathing becomes difficult, move to fresh air, and contact a physician.

OTHER HEALTH INFORMATION: Poly (acetyl) glucosamine can be characterized as a biologically safe, nontoxic, biocompatible and biodegradable polysaccharide. The publicly available toxicology and safety data adequately support the safety of poly (acetyl) glucosamine in terms of general toxicity in animals and in *in vitro* and local tolerance studies. A series of general toxicology tests were also conducted to provide additional assurance that poly (acetyl, arginyl) glucosamine did not show

differences from the safety profile of poly (acetyl) glucosamine. The results from these studies in rodents showed no test article-related changes in hematology or clinical chemistry, and no microscopic lesions associated with administration of poly (acetyl, arginyl) glucosamine. In a L5178Y TK^{+/-} mouse lymphoma forward mutation screen, poly (acetyl, arginyl) glucosamine was also negative for induction of mutagenic activity after treatment for 4 hours with and without S9, and for 24 hours without S9.

IV. AGENCY CONCLUSIONS:

The information submitted in support of this request for SYNOPLEX for addition to the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species (Index) for topical application on animals in the family Elephantidae and Rhinocerotidae for treatment of foot and dermal lesions infected with aerobic or facultative anaerobic Gram-positive and/or Gram-negative bacteria; and for treatment of sterile chronic foot and dermal lesions 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 on elephants and rhinoceroses 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 SYNOPLEX 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 SYNOPLEX for topical use on elephants and rhinoceroses.

C. MARKETING STATUS:

In its written report, the qualified expert panel recommended that SYNOPLEX 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:

1 gram bottle; 1 and 5 pack carton; and package insert