Date of Index Listing: November 23, 2015

FREEDOM OF INFORMATION SUMMARY

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

MIF 900-018

OXAPEX IDX

(hemoglobin crosfumaril (bovine) injection)

Captive mustelids, captive rodents, raptors, and captive or pet birds of the orders Psittaciformes, Passeriformes, and Columbiformes, excluding squab raised for food

"For the treatment of anemia; specifically hypoxemia associated with imminent anemic crisis caused by blood loss, hemolysis, or reduced hematopoiesis in captive mustelids, captive rodents, raptors, and captive or pet birds of the orders Psittaciformes, Passeriformes, and Columbiformes, excluding squab raised for food."

Requested by:

New A Innovation Limited

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I. GENERAL INFORMATION:

A. File Number: MIF 900-018

B. Requestor:

New A Innovation Limited
17/F
Chevalier Commercial Centre
8 Wang Hoi Road
Kowloon Bay, Kowloon
Hong Kong

U.S. Agent:
James H. Schafer, DVM
Schafer Veterinary Consultants, LLC
800 Helena Court
Fort Collins, CO 80524

C. Proprietary Name(s): OXAPEX IDX

D. Established Name(s): Hemoglobin crosfumaril (bovine) injection

E. Pharmacological Category: Hemoglobin-based oxygen carrier

F. Dosage Form(s): Injectable solution

G. Amount of Active Ingredient(s): 1.3 g (6.5%) modified and stabilized bovine Hb per 20 mL bag

H. How Supplied: 20 mL multi-layered plastic (ethylene vinyl acetate/ethylene vinyl alcohol) infusion bags

I. How Dispensed: By prescription (Rx)

J. Dosage(s): 5-10 mL/kg (0.5 to 1.0 mL/100 grams) of body weight administered as a slow bolus or at a rate of up to 1-3 mL/kg/hour

K. Route(s) of Administration: Intravenous or intraosseous

L. Species/Class(es): Captive mustelids, captive rodents, raptors, and captive or pet birds of the orders Psittaciformes, Passeriformes, and Columbiformes, excluding squab raised for food

M. Indication(s): For the treatment of anemia; specifically hypoxemia associated with imminent anemic crisis caused by blood loss, hemolysis, or reduced hematopoiesis in captive mustelids, captive rodents, raptors, and captive or pet birds of the orders Psittaciformes, Passeriformes, and Columbiformes, excluding squab raised for food.

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 OXAPEX IDX, for the treatment of anemia; specifically hypoxemia associated with imminent anemic crisis caused by blood loss, hemolysis, or reduced hematopoiesis in captive mustelids, captive rodents, raptors, and captive or pet birds of the orders Psittaciformes, Passeriformes, and Columbiformes, excluding squab raised for food, to determine whether the benefits of using OXAPEX IDX for the proposed use outweigh its risks to the target animals. The members of the qualified expert panel were:

Terry W. Campbell, DVM, PhD (Panel Leader), Colorado State University;

Krystan R. Grant, DVM, PhD Candidate, Colorado State University;

Cheryl B. Greenacre, DVM, DABVP, University of Tennessee;

Angela M. Lennox, DVM, DABVP, Avian and Exotic Animal Clinic of Indianapolis;

Marla K. Lichtenberger, DVM, DACVECC, Milwaukee Emergency Center for Animals.

A. FINDINGS OF THE QUALIFIED EXPERT PANEL:

Based on a thorough review of the literature, data from two pharmacokinetics studies, and their own personal experience, the qualified expert panel concluded that benefits of using OXAPEX IDX for the treatment of anemia; specifically hypoxemia associated with imminent anemic crisis caused by blood loss, hemolysis, or reduced hematopoiesis in captive mustelids, captive rodents, raptors, and captive or pet birds of the orders Psittaciformes, Passeriformes, and Columbiformes, excluding squab raised for food, outweigh the risks to the target animals.

The qualified expert panel agrees with the literature that anemia is common in avian species and small mammals (Hunter *et al*., 1997; Leighton *et al*., 1983; Nakade *et al*., 2005; Stuht *et al*., 1999; Dusek *et al*., 2004; Yamato *et al*., 1996; Dean *et al*., 2006; Joyner *et al*., 2006; Lichtenberger, 2007; Murray and Tseng, 2008; Nevill, 2009; Dube *et al*., 2011; Shaw *et al*., 2009, Johnston *et al*., 2007; Hawkey *et al*., 1982; Martinho, 2009; Bernard *et al.*, 1983; Sherrill and Gorham, 1985; Lichtenberger, 2004; Garner *et al.*, 2007; Pollock, 2007; Ammersbach *et al.*, 2008; Perpiñán *et al.*, 2008; Perpiñán and López, 2008; Campbell and Grant, 2010; Johnson-Delany, 2010; Malka *et al.*, 2010; Okey and Greaves, 1939; Yamanaka *et al.*, 1967; Elko and Cantrell, 1968; Ostwald *et al.*, 1971; Zucker *et al*., 1977; Reeves *et al.*, 2005; Chen *et al.*, 2006; Pyatskowit and Prohaska, 2008).

Treatment of anemia with whole blood transfusion is often difficult in these animals for various reasons such as: availability of compatible donor animals, cross matching, blood typing, the effort to appropriately screen for disease, or the potential of compromising the donor (Day 2003; Chen *et al*., 2009; Lichtenberger, 2004). Due to the challenges posed by whole blood transfusion, the qualified expert panel believes that having an oxygen-carrying substitute, such as OXAPEX IDX, available for use by veterinarians would be beneficial to the health of avian species and small mammals.

The risk-benefit analysis performed by the qualified expert panel to determine the target animal safety and effectiveness of OXAPEX IDX centered on a comparison of OXAPEX IDX to a similar hemoglobin-based oxygen carrier (HBOC) named OXYGLOBIN

(hemoglobin glutamer-200 (bovine), NADA 141-067). This approach was used because OXAPEX IDX was not available in the United States prior to addition of the drug to the Index.

After a detailed comparison of the two drug products, the qualified expert panel concluded that in its origin from bovine hemoglobin, physiological properties, chemical composition, clinical use, and administration, OXAPEX IDX appears to be similar to OXYGLOBIN. One difference between the two drug products is that OXYGLOBIN is considered a blood substitute and volume expander, whereas OXAPEX IDX is an oxygen transport agent and is not intended for volume expansion. If volume expansion is indicated in an animal being treated with OXAPEX IDX, fluids should be administered concurrently.

Other characteristics of OXAPEX IDX that differ from OXYGLOBIN, which the qualified expert panel believes will be favorable for OXAPEX IDX use in small mammals and avian species, are a smaller average molecular weight (85% 65 kDa), a lower concentration of hemoglobin (6.5 g/dL), and the smaller volume packaging (20 mL infusion bags). Lower concentrations of OXYGLOBIN were more effective during resuscitation in a hamster model (Cabrales *et al*., 2009), thereby suggesting that the lower concentration of hemoglobin in OXAPEX IDX may be beneficial.
Vasoconstriction likely played a role in the decreased oxygen delivery with the higher concentration of OXYGLOBIN in the same hamster study, which may not be an issue with OXAPEX IDX due to the smaller molecular weight. Also, OXAPEX IDX is supplied in 20 mL bags, which is a smaller package size. The smaller volume of drug is compatible with size of animals being treated and allows for less waste.

Another difference between the two drug products that may affect oxygen delivery to tissues in small mammals is the P_{50} or affinity for oxygen. OXAPEX IDX has a slightly higher P_{50} (decreased affinity for oxygen) which may increase oxygen delivery. An HBOC with an increased affinity for oxygen (lower P_{50}) would make oxygen unloading more difficult for smaller mammals. However, in microcirculation, it has been suggested that HBOCs with a higher P_{50} may unload more oxygen in the arterioles thereby not reaching the capillaries to deliver to the desired tissue (Tsai and Intaglietta, 2002).

In addition to their detailed comparison of the properties and composition of the two drug products, the qualified expert panel also reviewed the findings of two pharmacokinetics studies which compared OXAPEX IDX and OXYGLOBIN. The first study was conducted in dogs and demonstrated that both products are well tolerated when administered as a single intravenous injection of 1950 mg/kg (30 mL/kg OXYGLOBIN and 15 mL/kg OXAPEX IDX). These dosage levels represented the high end of the recommended dosage range for OXYGLOBIN and 1.5 to 3 times the proposed dose range for OXAPEX IDX. Two groups of six Beagles (three males and three females) were treated with either OXAPEX IDX or OXYGLOBIN on Day 1 and then received the other drug product on Day 18. There were no differences observed in vital signs, food consumption, body weight, or body condition between the treatment groups. There were three isolated incidents of ptyalism, one report of emesis, a variety of minor electrocardiographic changes (four T wave changes, three increased R waves, one second degree A-V block), and increased respiratory rate in one dog at the end of the study period compared to baseline.
These changes were considered to be isolated incidents and not related to the treatments.

The second study was conducted in rats and had a negative control group, a group treated with OXYGLOBIN, and a group treated with OXAPEX IDX. Both treated groups received an intravenous dose of 0.2 g/kg of their respective drug. Hemoglobin concentration and oxygen partial pressure were measured at 1, 6, 24, and 48 hours post-treatment. The elimination half-lives of OXAPEX IDX and OXYGLOBIN were similar in treated rats. Hemoglobin concentrations were also similar between the two treatment groups at each recording but higher in the treatment groups compared to the control group at 1 and 6 hours post-treatment. The partial pressure of oxygen was similar in the control and OXYGLOBIN-treated groups before treatment (higher than the OXAPEX IDX-treated group) and was significantly higher in the OXAPEX IDX-treated group compared to the OXYGLOBIN-treated group at 6 and 24 hours post-treatment.

Based on the findings of the two pharmacokinetics studies, the qualified expert panel concluded that OXAPEX IDX and OXYGLOBIN are similar with respect to hemoglobin concentration and clinical effects in dogs and rats, and that OXAPEX IDX treated rats have an increased partial pressure of oxygen up to 24 hours post-dose.

The qualified expert panel also conducted an extensive review of available literature and took into consideration their own experience with the use of HBOCs in the target species as part of their analysis. Most of the literature, as well as the expert panel's experience, relates specifically to the use of OXYGLOBIN. The panel states that OXYGLOBIN has been used extensively in small mammals and avian species with no reported adverse effects and, in many cases, for successful resuscitation of the patient (Lichtenberger, 2007).

The result of the qualified expert panel's risk-benefit analysis was a unanimous conclusion that OXAPEX IDX is safe and effective for use as a treatment for anemia in small mammal and avian species at the proposed dosage of 5-10 mL/kg or a slow bolus of 1-3 mL/kg/hour. The qualified expert panel also recommended that OXAPEX IDX be marketed by prescription.

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III. USER SAFETY:

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

"Not for use in humans. Keep out of reach of children. In case of accidental human injection, a physician should be consulted. In case of skin or eye contact, flush affected area with water."

IV. AGENCY CONCLUSIONS:

The information submitted in support of this request for OXAPEX IDX for addition to the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species (Index) for the following intended use satisfies the requirements of section 572 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 516:

For the treatment of anemia; specifically hypoxemia associated with imminent anemic crisis caused by blood loss, hemolysis, or reduced hematopoiesis in captive mustelids, captive rodents, raptors, and captive or pet birds of the orders Psittaciformes, Passeriformes, and Columbiformes, excluding squab raised for food.

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 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 OXAPEX IDX 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 OXAPEX IDX for the treatment of anemia; specifically hypoxemia associated with imminent anemic crisis caused by blood loss, hemolysis, or reduced hematopoiesis in captive mustelids, captive rodents, raptors, and captive or pet birds of the orders Psittaciformes, Passeriformes, and Columbiformes, excluding squab raised for food.

C. MARKETING STATUS:

OXAPEX IDX will be marketed by prescription.

D. EXCLUSIVITY:

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

E. ATTACHMENTS:

Facsimile Labeling:

20 mL bag