FREEDOM OF INFORMATION SUMMARY

Oxyglobin® Solution

NADA # 141-067

Sponsor: BIOPURE Corporation
11 Hurley Street
Cambridge, MA 02141

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FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

NADA Number: 141-067

Sponsor: Biopure Corporation
11 Hurley Street
Cambridge MA 02141

Generic Name: Hemoglobin glutamer-200 (bovine)

Trade Name: Oxyglobin® Solution

Marketing Status: Rx: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Effect of the supplement: This supplement changes the original approval from a fixed dosage of 30 mL/kg to a flexible dosage range of 10-30 mL/kg.

2. INDICATIONS FOR USE:

Oxyglobin® is indicated for the treatment of anemia in dogs by increasing systemic oxygen content (plasma hemoglobin concentration) and improving the clinical signs associated with anemia, regardless of the cause of anemia (hemolysis, blood loss, or ineffective erythropoiesis).

3. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND RECOMMENDED DOSAGE:

Oxyglobin® is a sterile, clear, dark purple solution containing 13 g/dL purified, polymerized hemoglobin of bovine origin in a modified Lactated Ringer's Solution.

DOSAGE FORM: Injectable

ROUTE OF ADMINISTRATION: Intravenous at a rate of up to 10 mL/kg/hr

DOSAGE AND ADMINISTRATION:

The recommended dosage of Oxyglobin® is a one-time dose of 10-30 mL/kg of body weight administered intravenously at a rate of up to 10 mL/kg/hr. The choice of dose within the recommended range will vary with the patient and the clinical situation.

Pharmacokinetic data show that there is an increase in the duration of action with increasing dose.

4. EFFECTIVENESS:

The effectiveness of Oxyglobin® at the lower dose was established by the following studies:

LABORATORY TISSUE OXYGENATION STUDY

A) Title: Correction of tissue hypoxia associated with acute normovolemic anemia: A comparison of polymerized bovine-derived hemoglobin and erythrocytes in a canine model

B) Principal Investigator: Thomas G. Standl, MD
Eppendorf University Hospital
Martinistrasse 52
20246 Hamburg,
Germany

C) Design of Study:

1) Purpose of Study: To examine skeletal muscle tissue oxygen tension after severe acute normovolemic anemia, comparing the effects of cumulative equivalent doses of hemoglobin in the form of stored red cells, freshly donated blood and polymerized bovine hemoglobin in a canine model.

2) Test Animals: 24 Foxhounds divided into 3 groups of 8 dogs each.

3) Groups: Group 1:Banked red blood cells (stored for 3 weeks)
Group 2: Fresh blood
Group 3: HBOC-201 (HBOC- hemoglobin based oxygen carrier)

4) Methods: Acute normovolemic hemodilution model: for each dog, blood was withdrawn and simultaneously replaced with 6% hetastarch to target hematocrit values of 20%, 15% and 10% while maintaining pulmonary capillary wedge pressure.

5) Dosage Form: Injectable

Biopure has developed two different HBOC formulations, HBOC-201, and HBOC-301, Oxyglobin®. The two solutions are similar with the exception of the absolute molecular weight distribution. They are both based on an ultra-purified, glutaraldehyde polymerized, bovine hemoglobin in a modified Lactated Ringers buffer. The processing steps are similar with the exception of a final filtration step for HBOC-201 to remove low molecular weight hemoglobin. There are no differences in the oxygen binding and release characteristics of the two products as shown by nearly identical equilibrium curves for HBOC-201 and Oxyglobin®.

6) Route of Administration: Intravenous

7) Dosage Used: 3 stepwise infusions of hemoglobin to achieve a cumulative augmentation of 1, 2 and 3 g/dL total plasma hemoglobin

8) Test Duration: Group 1 dogs were phlebotomized (15 mL/kg) 3 weeks prior to treatment and the RBCs were stored. All dogs were hemodiluted immediately prior to treatment. The study was terminated on Day 1.

9) Pertinent Parameters: Skeletal muscle oxygen tension immediately following dosing.

D) Results:

In the dogs receiving HBOC-201, the mean baseline tissue oxygenation was restored by a hemoglobin augmentation of 0.7g/dL.

E) Conclusions:

The study results indicate that an increase in total hemoglobin by as little as 0.7 g/dL with HBOC-201 in plasma was associated with restoration of baseline tissue oxygen tension after severe hypoxia due to hemodilution.

PHARMACOKINETICS STUDY

A) Title: Noncompartmental pharmacokinetic analysis of plasma

hemoglobin data from Study 2022-97

B) Principal Investigator:

Nancy Kelly, DVM DABT
ITR Laboratories
19601 Clark Graham
Baie d' Urfe, Quebec
Canada H9X 3T1

C) Design of Study:

1) Purpose of Study:	To determine the pharmacokinetics of Oxyglobin® following a single intravenous infusion in a model of acute isovolemic hemodilution.
2) Test Animals:	18 Beagle dogs divided into 3 groups of 6 dogs each.
3) Control:	None
4) Diagnosis:	Acute isovolemic hemodilution model: blood was withdrawn and simultaneously replaced with Lactated Ringer's Solution to a target hematocrit of 15% while maintaining central venous pressure.
5) Dosage Form:	Injectable. The formulation HBOC-301, Oxyglobin®, was used in this study.
6) Route of Administration:	Intravenous
7) Dosage Used:	7, 10, 15 mL/kg
8) Test Duration:	Dogs were hemodiluted immediately prior to infusion. Blood was collected within 1 minute after the completion of the infusion and at 1, 3, 6, 12, 18, 24 and 30 hours post infusion and twice daily until Day 7.
9) Pertinent Parameters:	Total plasma hemoglobin concentration

D) Results:

The following table contains a summary of the pharmacokinetic parameters:

Dose mL/kg	Duration (hours)*: oxyglobin levels over 1 g/dL	Terminal half-life (hours)*
7	4 - 9	17-25
10	11 - 23	18-26
15	23 - 39	19-30

*range based on mean ±SD

E) Conclusions:

In this study, an Oxyglobin® (hemoglobin based oxygen carrier) dose of 10 mL/kg provides a 1 g/dL plasma hemoglobin level for 11 to 23 hours.

CONCLUSIONS REGARDING EFFECTIVENESS

1. The laboratory tissue oxygenation study shows that augmentation of plasma hemoglobin concentration by as little as 0.7 g/dL with a hemoglobin based oxygen carrier in plasma restores tissue oxygenation to baseline levels.

2. The pharmacokinetics study shows that an Oxyglobin® (hemoglobin based oxygen carrier) dose of 10 mL/kg can provide 1 g/dL plasma hemoglobin.

3. Together, these studies support the effectiveness of 10 mL/kg of Oxyglobin® as the lower end of the dosage range.

5. SAFETY:

The safety of Oxyglobin® is based on data in the original approval (refer to the Freedom of Information Summary dated January 12, 1998.) This supplement provides a lower dose range than in the original approval.

6. HUMAN SAFETY:

Human Safety Relative to Food Consumption: Data on human safety, pertaining to consumption of drug residues in food, were not required. This drug is to be labeled for use in dogs which are non-food animals.

Human Safety Relative to Possession, Handling, and Administration: labeling contains an adequate caution statement.

7. AGENCY CONCLUSIONS:

The data in support of this supplemental NADA comply with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations, and demonstrate that Oxyglobin® (hemoglobin glutamer-200 (bovine)) when used under labeled conditions of use, is safe and effective.

Under section 512(c)(2)(F)(iii) of the FFDCA, this approval for non food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the application contains substantial evidence of the effectiveness of the drug involved, or studies of animal safety required for the approval of the application conducted or sponsored by the applicant.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise and proper diagnosis are required to: 1) determine the need for oxygen carrying support, 2) use a drug intended for intravenous infusion which requires close monitoring and possible adjustment of infusion rate, and 3) recognize and treat, if necessary, adverse reactions to the drug.

The following patents claim Oxyglobin®: 5,084,558 (exp. 1/28/09), 5,296,465 (exp. 3/22/11) and 5,618,919 (exp. 4/8/14).

8. LABELING (attached)

a. Package insert (draft)

Labels for the bag overwrap, carton, and shipper were not changed by this supplemnetal approval.