ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Oxyglobin 130 mg/mL solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Active substance

Haemoglobin glutamer-200 (bovine) – 130 mg/mL

2.2 Excipients knowledge of which is essential for the proper administration of the veterinary medicinal product

Modified Lactated Ringer's Solution containing the standard components: water for injection, NaCl, KCl, $CaC1_2\,2H_2O$, NaOH, sodium lactate and also N-acetyl-l cysteine.

3. PHARMACEUTICAL FORM

Solution for infusion

4. PHARMACOLOGICAL PROPERTIES

Oxyglobin is a haemoglobin-based oxygen carrying fluid that increases plasma and total haemoglobin concentrations and thus increases arterial oxygen content. The plasma half-life is 30-40 hours. It is eliminated from the plasma in 5-7 days.

Metabolism and excretion: Haemoglobin dissociates in plasma and is progressively incorporated in the protein pool of the organism. Haeme degrades according to common pathways leading to bilirubin and bile pigments. A small amount of unstabilised tetrameric haemoglobin (<5%) may be excreted through the kidneys, resulting in transient haemoglobinuria for < 4 hours.

5. CLINICAL PARTICULARS

5.1 Target species

Dogs

5.2 Indication for use, specifying the target species

Oxyglobin provides oxygen carrying support to dogs improving the clinical signs of anaemia for at least 24 hours, independent of the underlying condition.

5.3 Contra-indications

Animals previously treated with Oxyglobin.

Plasma volume expanders, such as Oxyglobin, are contraindicated in dogs predisposed to circulatory overload with conditions such as oliguria or anuria or advanced cardiac disease (i.e., congestive heart failure) or otherwise severely impaired cardiac function. Oxyglobin is intended for single administration only.

5.4 Undesirable effects (frequency and seriousness)

Adverse events related to Oxyglobin and/or the underlying disease causing anaemia have been observed. Undesirable effects include mild to moderate yellow/orange discoloration of the skin, mucous membranes, sclera, dark faeces and discoloured or turbid urine due to metabolism and/or excretion of haemoglobin. A commonly observed undesirable effect was circulatory overload with associated clinical signs such as tachypnea, dyspnea, harsh lung sounds and pulmonary edaema. Adverse effects commonly seen were vomiting, a loss of appetite, and fever. Occasionally noted adverse events were diarrhoea, cardiac arrhythmias and very rarely nystagmus.

5.5 Special precautions for use

Concomitant treatment of the cause of the anaemia should be instituted.
The animal should not be over-hydrated prior to administration. Due to the plasma expanding properties of Oxyglobin, the possibility of circulatory overload and pulmonary oedaema should be considered especially when administering adjunctive intravenous fluids, particularly colloidal solutions. Signs of circulatory overload should be carefully monitored or central venous pressure (CVP) measured (increase in CVP has been recorded in all treated dogs in which it was measured).

Circulatory overload may be controlled by slowing the rate of administration.

Treatment with Oxyglobin results in a mild decrease in PCV (packed cell volume) immediately post infusion.

The safety and efficacy of Oxyglobin have not been evaluated in dogs with thrombocytopenia with active bleeding, oliguria or anuria, or advanced cardiac disease.

Clinical Pathology

Chemistry*:* The presence of Oxyglobin in serum may interfere with colorometric readings and result in artifactual increases or decreases in the results of serum chemistry tests depending on the dosage administered, the time since infusion, the type of analyzer and the reagents used. (Contact the distributor for specific data.)

Haematology: No interference. Confirm that haemoglobin is measured, not calculated from red blood cell number.

Coagulation: Prothrombin time (PT) and activated partial thromboplastin time (aPTT) can be accurately determined using methods that are mechanical, magnetic, and light scattering. Optical methods are not reliable for coagulation assays in the presence of Oxyglobin.

Urinalysis: Sediment examination is accurate. Dipstick measurements (i.e., pH, glucose, ketones, protein) are inaccurate while gross discolouration of the urine is present.

5.6 Use during pregnancy and lactation

The safety of Oxyglobin for use in pregnant or lactating bitches has not been determined.

5.7 Interaction with other veterinary medicinal products and other forms of interaction

None known

5.8 Posology and method of administration

The recommended dosage of Oxyglobin is 30 mL/kg of body weight administered intravenously at a rate up to 10 mL/kg/hr. Oxyglobin is intended for single administration.

In certain clinical situations, a dosage of 15-30 mL/kg may be appropriate. The optimum dosage is based upon the degree and chronicity of the anaemia and the desired duration of the effect. (See Table A Pharmacokinetic Parameters)

Table A: Pharmacokinetic Parameters at Multiple Dose Levels after a Single Infusion of Oxyglobin

Dose (mL/kg)	Immediate post infusion plasma concentration* (g/dL)	Duration (hours): Oxyglobin levels over 1 g/dL	Cleared from plasma (days)***
15	2.0 – 2.5	23 – 39	4 – 6
21	3.4 – 4.3	66 – 70	5 – 7
30	3.6 – 4.8	74 – 82	5 – 9**

* range based on mean ± SD

** range based on estimated mean value with bounds of a 95% prediction interval

***range based on 5 terminal half-lives

Remove overwrap prior to use. Use within 24 hours. Oxyglobin should be administered using aseptic technique via a standard intravenous infusion set and catheter.

As with any intravenous fluid administration, Oxyglobin should be warmed to 37° C prior to administration. Do not microwave. Do not overheat.

Use of Oxyglobin does not require typing or cross–matching of the recipient's blood.

5.9 Overdose (symptoms, emergency procedures, antidotes)

Overdosage or an excessive rate of administration (i.e., >10 mL/kg/hr) could result in immediate cardiopulmonary effects, in which case infusion of Oxyglobin should be discontinued immediately until signs abate. Treatment of circulatory overload may be necessary.

5.10 Special warnings for each target species

None

5.11 Withdrawal period

Not applicable

5.12 Special precautions to be taken by the person administering the veterinary medicinal product to animals

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities (major)

Do not administer with other fluids or medicinal products concurrently via the same infusion set. Do not add medications or other solutions to the bag. Do not combine the contents of more than one bag.

6.2 Shelf life, when necessary after reconstitution of the veterinary medicinal product or when the container is opened for the first time

3 years

In-use shelf-life: 24 hours

6.3. Special precautions for storage

Do not store above 30°C. Do not freeze. Use within 24 hours of removing overwrap.

6.4 Nature and contents of container

A box with two (2) polyolefin infusion bags (125 mL), each within an overwrap.

6.5 Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from such medicinal products, if appropriate

Any unused product or waste material should be disposed of in accordance with local requirements.

7. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Biopure Netherlands B.V.
Prinses Irenestraat, 59
NL-1077-WV Amsterdam

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

B. PACKAGE INSERT

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Oxyglobin 130 mg/mL Solution for infusion

2. STATEMENT OF THE ACTIVE SUBSTANCE

Hemoglobin glutamer-200 (bovine) – 130 mg/mL

3. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Marketing Authorisation Holder:
Biopure Netherlands B.V.
Prinses Irenestraat, 59
NL-1077-WV Amsterdam

Manufacturing Authorisation responsible for Batch Release:
Dales Pharmaceutical Ltd.
Snaygill Industrial Estate
Keighley Road
Skipton
North Yorkshire, BD23 2RW
United Kingdom

4. TARGET SPECIES

For dogs

5. INDICATION

Oxyglobin provides oxygen carrying support to dogs improving the clinical signs of anaemia for at least 24 hours independent of the underlying condition.

6. DOSAGE FOR EACH SPECIES

The recommended dosage of Oxyglobin is 30 mL/kg of body weight administered intravenously at a rate up to 10 mL/kg/hr. In certain clinical situations, a dosage of 15-30 mL/kg may be appropriate. The optimum dosage is based upon the degree and chronicity of the anemia and the desired duration of the effect. (See Table A Pharmacokinetic Parameters)

Table A: Pharmacokinetic Parameters at Multiple Dose Levels after a Single Infusion of Oxyglobin

Dose (mL/kg)	Immediate post infusion plasma concentration* (g/dL)	Duration (hours): Oxyglobin levels over 1 g/dL	Cleared from plasma (days)***
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21	3.4 – 4.3	66 – 70	5 – 7
30	3.6 – 4.8	74 – 82	5 – 9**

* range based on mean ± SD

** range based on estimated mean value with bounds of a 95% prediction interval

*** range based on 5 terminal half-lives

7. METHOD AND ROUTE OF ADMINISTRATION

Oxyglobin is intended for a single intravenous administration by infusion.

8. ADVICE ON CORRECT ADMINISTRATION

Remove overwrap prior to use. Use within 24 hours. Oxyglobin should be administered using aseptic technique via a standard intravenous infusion set and catheter. As with any intravenous fluid administration, Oxyglobin should be warmed to 37° C prior to administration. Do not microwave. Do not overheat.

Do not administer with other fluids or medicinal products concurrently via the same infusion set. Do not add medications or other solutions to the bag. Do not combine the contents of more than one bag.

9. CONTRA-INDICATIONS

Plasma volume expanders, such as Oxyglobin, are contraindicated in dogs predisposed to circulatory overload with conditions such as oliguria or anuria or advanced cardiac disease (i.e., congestive heart failure) or otherwise severely impaired cardiac function.

10. UNDESIRABLE EFFECTS

During the clinical safety and efficacy study, adverse events were seen which may have been related to Oxyglobin and/or the underlying disease causing anaemia. Side effects which were observed included mild to moderate discolouration of the mucous membranes, sclera, and urine due to metabolism and/or excretion of haemoglobin. Effects commonly seen were vomiting, loss of appetite, fever, and circulatory overload with associated clinical signs such as tachypnea, dyspnea, harsh lung sounds, and pulmonary edaema; circulatory overload was controlled by slowing the rate of administration. Occasionally noted effects were diarrhoea, discolouration of the skin, cardiac arrhythmias and very rarely nystagmus.

11. WITHDRAWAL PERIOD

Not applicable

12. SPECIAL STORAGE CONDITIONS, IF ANY

Do not store above 30°C. Do not freeze. Use within 24 hours of removing overwrap.

13. SPECIAL WARNINGS, IF NECESSARY

Do not use in animals previously treated with Oxyglobin.

Concomitant treatment of the cause of the anaemia should be instituted.

The animal should not be over-hydrated prior to administration. Due to the plasma expanding properties of Oxyglobin, the possibility of circulatory overload should be considered especially when administering adjunctive intravenous fluids, particularly colloidal solutions. Signs of circulatory overload should be carefully monitored or central venous pressure (CVP) measured. If CVP increases to a clinically unacceptable level and/or if signs of circulatory overload are observed, the infusion of Oxyglobin should be temporarily discontinued and re-instituted at a slower rate when signs abate and/or CVP decreases.

Treatment with Oxyglobin results in a mild decrease in PCV (packed cell volume) immediately post infusion.

The safety and efficacy of Oxyglobin have not been evaluated in dogs with, thrombocytopenia with active bleeding, oliguria or anuria, or advanced cardiac disease.

The safety of Oxyglobin for use in pregnant or lactating bitches has not been determined. The use in such animals is not recommended.

14. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED VETERINARY MEDICINAL PRODUCT OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS IF APPROPRIATE

Any unused product or waste material should be disposed of in accordance with local requirements.

15. DATE ON WHICH THE PACKAGE INSERT WAS LAST REVISED

16. OTHER INFORMATION

Clinical Pathology

Chemistry: The presence of Oxyglobin in serum may interfere with colorometric readings and result in artifactual increases or decreases in the results of serum chemistry tests depending on the dosage administered, the time since infusion, the type of analyzer and the reagents used. (Contact the distributor for specific data.)

Haematology: No interference. Confirm that haemoglobin is measured, not calculated from red blood cell number.

Coagulation: Prothrombin time (PT) and activated partial thromboplastin time (aPTT) can be accurately determined using methods that are mechanical, magnetic, and light scattering. Optical methods are not reliable for coagulation assays in the presence of Oxyglobin.

Urinalysis: Sediment examination is accurate. Dipstick measurements (i.e., pH, glucose, ketones, protein) are inaccurate while gross discolouration of the urine is present.