ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Oxyglobin 130 mg/ml solution for infusion for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Haemoglobin glutamer-200 (bovine) – 130 mg/ml

Excipients:

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs

4.2 Indications 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.

4.3 Contraindications

Do not use in 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.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals

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 oedema 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 analyser 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.

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

Not applicable.

4.6 Adverse reactions (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 oedema. Adverse effects commonly seen were vomiting, a loss of appetite, and fever. Occasionally noted adverse events were diarrhoea, cardiac arrhythmias and very rarely nystagmus.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

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

4.8 Interaction with other medicinal products and other forms of interaction

None known.

4.9 Amounts to be administered and administration route

The recommended dosage of Oxyglobin is 30 ml/kg of body weight administered intravenously at a rate up to 10 ml/kg/h. 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 postinfusion 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.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

Overdosage or an excessive rate of administration (i.e., >10 ml/kg/h) 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.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Blood substitutes, ATCvet code: QB05AA10.

5.1 Pharmacodynamic 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.

5.2 Pharmacokinetic particulars

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Modified Lactated Ringer's Solution containing the standard components: Water for injection,

NaCl
KCl
$CaC1_2$ $2H_2O$
NaOH
Sodium lactate
N-acetyl-l cysteine

6.2 Major incompatibilities

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.

6.3 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale:
60 ml - 3 years
125 ml - 5years

Shelf-life after first opening the immediate packaging: 24 hours.

6.4. Special precautions for storage

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

6.5 Nature and composition of immediate packaging

A box with one (1) polyolefin infusion bag (containing either 60 ml or 125 ml), within an overwrap.
Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

OPK Biotech Netherlands BV
Herikerbergweg 88
1101CM
Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER

EU/2/99/015/003
EU/2/99/015/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29/11/1999
Date of last renewal: 01/10/2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS OF THE MARKETING AUTHORISATION REGARDING SUPPLY OR USE

C. CONDITIONS OR RESTRICTIONS OF THE MARKETING AUTHORISATION WITH REGARD TO SAFE AND EFFECTIVE USE

D. STATEMENT OF THE MRLs

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance
OPK Biotech LLC
39 Hurley Street
Cambridge
MA 02141
USA

Name and address of the manufacturer responsible for batch release
Dales Pharmaceutical Ltd. Snaygill Industrial Estate Keighley Road
Skipton
North Yorkshire BD23 2RW
United Kingdom

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS OF THE MARKETING AUTHORISATION REGARDING SUPPLY OR USE

To be supplied only on veterinary prescription.

C. CONDITIONS OR RESTRICTIONS OF THE MARKETING AUTHORISATION WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE PRODUCT

Not applicable.

D. STATEMENT OF THE MRLs

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Oxyglobin 130 mg/ml solution for infusion for dogs

2. STATEMENT OF ACTIVE SUBSTANCES

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

3. PHARMACEUTICAL FORM

Solution for infusion

4. PACKAGE SIZE

60 ml infusion bag

125 ml infusion bag

5. TARGET SPECIES

Dogs

6. INDICATION(S)

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

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oxyglobin is intended for single intravenous administration by infusion.

8. WITHDRAWAL PERIOD(S)

Not applicable.

9. SPECIAL WARNING(S), IF NECESSARY

Do not microwave. Do not overheat > 37 °C.
Excessive administration rate (>10 ml/kg/h) may result in circulatory overload.

10. EXPIRY DATE

<EXP {month/year}>

11. SPECIAL STORAGE CONDITIONS

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

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, if applicable

For animal treatment only - to be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the reach and sight of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

OPK Biotech Netherlands BV
Herikerbergweg 88
1101CM Amsterdam
The Netherlands

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/99/015/003 60 ml
EU/2/99/015/004 125 ml

17. MANUFACTURER'S BATCH NUMBER

<Batch> <Lot> {number}

B. PACKAGE LEAFLET

PACKAGE LEAFLET:
Oxyglobin 130 mg/ml solution for infusion for dogs

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:
OPK Biotech Netherlands BV
Herikerbergweg 88
1101CM, Amsterdam
The Netherlands

Manufacturer for the batch release:
Dales Pharmaceutical Ltd.
Snaygill Industrial Estate
Keighley Road
Skipton
North Yorkshire, BD23 2RW
United Kingdom

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Oxyglobin 130 mg/ml solution for infusion for dogs

3. STATEMENT OF THE ACTIVE SUBSTANCE AND OTHER INGREDIENTS

Haemoglobin glutamer-200 (bovine) – 130 mg/ml.

4. INDICATION(S)

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

5. CONTRAINDICATIONS

Do not use in 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.

6. ADVERSE REACTIONS

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 oedema; 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.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

If you notice any serious effects or other effects not mentioned in this leaflet, please inform your veterinary surgeon.

7. TARGET SPECIES

Dogs

8. DOSAGE FOR EACH SPECIES, ROUTE(S) 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. 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

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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

9. 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.

10. WITHDRAWAL PERIOD(S)

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the reach and sight of children.
Do not store above 30 °C. Do not freeze. Use within 24 hours of removing overwrap. Do not use after the expiry date stated on the label.

12. SPECIAL WARNING(S)

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.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

15. 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.

60 ml infusion bag.
125 ml infusion bag.

Not all pack sizes may be marketed.