Veterinary Medicines Directorate

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Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Oxmax 65 mg/ml Solution for Infusion for Dogs

Date Created: February 2024

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Oxmax 65 mg/ml Solution for Infusion for Dogs
Applicant	New Alpha Innovation Biopharmaceutical Ireland Limited The Black Church St. Mary's Place Dublin D07 P4AX
Active substance	Haemoglobin betafumaril (bovine)
ATC Vetcode	QB05AA91
Target species	Dogs
Indication for use	Indicated as an adjunct therapy in the management of canine haemorrhagic shock. A beneficial effect of treatment was demonstrated for 24 hour survival rate when Oxmax was administered concomitantly with low dose resuscitative fluids (Lactated ringer's solution).

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Full application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of conclusion of the procedure	28/11/2023

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC.[1] The product is safe for the user, and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy[2] of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains haemoglobin betafumaril (bovine) and the excipients N-acetyl-L-cysteine, sodium chloride, potassium chloride, calcium chloride dehydrate, sodium acetate trihydrate, sodium hydroxide, acetic acid and glacial and water for injection.

The container/closure system consists of an electron beam irradiated sterile IV multi-layer bag, wrapped in an aluminium overwrap pouch. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence of preservative are justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of: solubilisation, addition of excipients and filtration.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substance is haemoglobin betafumaril (bovine), a novel active substance. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

All excipients are described in Ph. Eur.

II.C.4. Substances of Biological Origin

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification. Control tests on the finished product are those for: appearance, total Hb, met Hb, Oxy Hb, DMW, pH, particulate, contamination, sterility, endotoxin, NAC and osmolarity.

II.F. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.
Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after first opening the immediate packaging: use immediately.

Store in a refrigerator (2°C - 8°C)
Do not freeze.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Studies have been conducted which show that haemoglobin betafumaril (bovine) acts like native Hb and is free in plasma. The applicant has also conducted studies which show that haemoglobin dissociates in plasma and is incorporated into the protein pool of the animal and is eliminated from the plasma in 5 days.

Toxicological Studies

The applicant has conducted laboratory studies as below.

Single Dose Toxicity

While single dose toxicity studies were not required as this application holds a MUMS status, the applicant provided three acute toxicity studies in rats. The studies showed that the product is well tolerated as a single dose and no adverse events were evident clinically.

Repeated Dose Toxicity

The applicant conducted a pilot repeat dose study to investigate the toxicity of the product following 3 repeated administrations at 48 hour intervals in the target species. The findings showed that the repeated treatment with the product is well tolerated in the target species. No NOEL could be established.

Genotoxicity
The mutagenic potential was investigated in two in vitro tests. In both test systems, there was no evidence that the product has mutagenic potential.

Studies of Other Effects

The applicant has conducted additional studies regarding interference with colorimetric assays which show that interference may be present. Additional information has been provided in the SPC.

Observations in Humans

Bibliographical data were provided which show that the product is unlikely to present a risk in terms of user safety.

User Safety

A user risk assessment was provided in compliance with the relevant guideline.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore the following applicant's user recommendations are appropriate:,

If adverse reactions develop following accidental self-administration, seek medical advice immediately and show the package leaflet or the label to the physician.

This product contains bovine-derived haemoglobin. There is a risk that immune mediated reactions (hypersensitivity reactions) may occur in sensitised persons if repeated accidental self-injection occurs. In case of hypersensitivity reactions, seek medical advice immediately and show the package leaflet or the label to the physician. Do not handle or administer the product if a previous hypersensitivity reaction has occurred.

Acetylcysteine is an excipient in this veterinary medicinal product and has been associated with hypersensitivity reactions in humans following intravenous infusion. People with known hypersensitivity to acetylcysteine should administer the veterinary medicinal product with caution.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

Phase I:

The product will only be used in non-food animals and as a result environmental exposure will be low. A Phase II ERA was not required.

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

The applicant has conducted studies describing the pharmacodynamic and pharmacokinetic properties of the active substance. The pharmacodynamic effect of the product is based on the oxygen carrying capability of the active substance. The pharmacokinetic studies show that the half life of the proposed dose is 17 hours and is metabolised and eliminated via known metabolic pathways of native Hb.

Tolerance in the Target Species

The applicant has conducted a controlled target animal tolerance study using multiples of the recommended dose in the target species. A placebo was used as a control. All doses were administered by intravenous injection on 1 occasion with varying dose volumes. It was concluded that, the product at doses up to 90 ml/kg is well tolerated.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

IV.II. Clinical Documentation

Laboratory Trials

The applicant has provided a dose determination study which show that an administration of 10 ml/kg of the product resulted in the most favourable profile with respect to measurements of resolution of oxygen debt. A pivotal dose confirmation study was presented.

Field Trials

No field trials have been conducted as in line with MUMS requirements.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics the benefit/risk profile of the product is favourable.

MODULE 4

POST- AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

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