ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

PropoFlo Plus, 10 mg/ml Emulsion for Injection for Dogs and Cats

PuAR correct as of 23/04/2018 when RMS was transferred to ES.
Please contact the RMS for future updates

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0179/003/MR
Name, strength and pharmaceutical form	PropoFlo Plus, 10 mg/ml Emulsion for Injection for Dogs and Cats
Applicant	Abbott Laboratories Ltd Abbott House Vanwall Business Park Vanwall Road Maidenhead Berkshire SL6 4XE UK
Active substance(s)	Propofol
ATC Vetcode	QN01AX10
Target species	Cats and Dogs
Indication for use	The veterinary medicinal product is indicated for therapeutic use in dogs and cats as a short-acting, intravenous general anaesthetic with a short recovery period: For procedures of short duration, lasting up to approximately 5 minutes. For induction of general anaesthesia where maintenance is provided by inhalation anaesthetic agents. For induction and short-term maintenance of general anaesthesia by administration of incremental doses of the product to effect for approximately half an hour (30 minutes), not to exceed the total dose in one anaesthetic episode of 24 mg/kg (2.4 ml/kg) of propofol in cats or dogs.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Extension application in accordance with Article 39 (1) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	21 March 2012.
Date product first authorised in the Reference Member State (MRP only)	15th December 2010.
Concerned Member States for original procedure	Austria, Belgium, Denmark, Finland, France, Germany, Iceland, Ireland, Italy, Luxembourg, The Netherlands, Norway, Portugal, Spain, Sweden.

I. SCIENTIFIC OVERVIEW

PropoFlo Plus, 10 mg/ml, Emulsion for Injection for Dogs and Cats is indicated for therapeutic use in dogs and cats as a short-acting, intravenous general anaesthetic with a short recovery period. Additionally, the product is to be used for procedures of short duration, lasting up to approximately 5 minutes. The product can also be used for induction of general anaesthesia where maintenance is provided by inhalation anaesthetic agents and for induction and short-term maintenance of general anaesthesia by administration of incremental doses to effect for approximately half an hour.

This is an application for an extension to the Marketing Authorisation for PropoFlo, 10 mg/ml Emulsion for Injection for Dogs and Cats, which has been marketed in the UK since 2002, for a change in formulation from single-dose, partial use, to multi-dose, submitted in accordance with Annex I of Regulations (EC) No 1234/2008 para 2 (d) as governed by Art 39 (1) Directive 2001/82/EC as amended by Directive 2004/28/EC.

The original reference product, with which essential similarity was claimed for the original product, is Rapinovet 10 mg/ml Emulsion for Injection, a product marketed by Schering-Plough Animal Health. Rapinovet was first authorised in the UK in December 1997.

The product should be administered intravenously and prior to use, it should be inspected visually for absence of particulate matter and discolouration. It has been shown that the product can be safely used in the target species.
Veterinarians are referred to the SPC for information regarding possible adverse reactions.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. 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 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. QUALITY ASPECTS

Quality data were originally supplied for PropoFlo, 10 mg/ml Emulsion for Injection for Dogs and Cats, and these data are included in this section. No further information for this extension application was required.

A. Composition

The product contains 10 mg/ml propofol and the excipients benzyl alcohol (E1519), soya-bean oil refined, purified egg phosphatides (egg lecithin), glycerol, oleic acid, sodium hydroxide and water for injections. The container/closure system consists of Type I glass vials with fluorinated polymer coated bromobutyl rubber stoppers and flip off aluminium/polypropylene seals. There are two pack sizes: 20 ml vials of product which each contain 200 mg propofol (propofol 10 mg/ml), 5 vials per carton, and 50 ml vials of product which each contain 500 mg propofol (propofol 10 mg/ml), 1 vial per carton. The particulars of the containers and controls performed are provided and conform to the regulation.

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

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is propofol, an established active substance described in the European Pharmacopoeia (Ph. Eur). The active substance is manufactured in accordance with the principles of good manufacturing practice, in accordance with Certificates of Suitability, R1-CEP 2001-267 – Rev 01, and R1-CEP-2001-188 Rev - 01.

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.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

Glycerol and lecithin, the only materials which may pose a TSE risk are not sourced from ruminant origin. An appropriate Format 3 declaration on TSE compliance was provided.

E. Control on intermediate products

Not applicable.

F. 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 sites have been provided demonstrating compliance with the specification.

G. 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.

Active substance

Data have been provided which indicate that the active substance is stable when stored in the appropriate container under appropriate conditions. The retest interval of 2 years is justified.

Finished Product

Data have been provided which indicate that the finished product is stable for 2 years.

In-Use

An in-use shelf-life of 28 days is justified.[1]

H. Genetically Modified Organisms

Not applicable.

J. Other Information

The application was supported with regard to quality. The following precautions are included on the SPC and product literature:

[1] In-use shelf life increased from 14 days to 28 days via a Variation Procedure 18th April 2011.

- This medicinal product does not require any special storage conditions.
- Do not freeze.
- Keep the container in the outer carton.

The finished product has a shelf-life of 3 years, and an in-use shelf-life of 28 days.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

PropoFlo Plus, 10 mg/ml, Emulsion for Injection for Dogs and Cats contains the active ingredient propofol, 10 mg/ml, in an oil-in-water emulsion. The product is essentially similar to the currently marketed product PropoFlo 10 mg/ml Emulsion for Injection for Dogs and Cats, except for the inclusion of benzyl alcohol at a level of 2% in the final formulation. Benzyl alcohol is included as a preservative, as PropoFlo Plus, 10 mg/ml, Emulsion for Injection for Dogs and Cats is a repeat dose formulation for cats and dogs.

The applicant has cross referred to the data originally supplied for PropoFlo 10 mg/ml Emulsion for Injection for Dogs and Cats and has only submitted data in support of use of benzyl alcohol in the formulation. This is considered acceptable.

Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users and the environment.

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics

Benzyl alcohol is a widely used antimicrobial preservative in cosmetics, foods and a wide range of pharmaceutical formulations, including oral and parenteral preparations at up to 2% w/v. Concentrations up to 3% are used in cosmetics and it may be used as a solubiliser at 5% or more while a 10% solution is used as a disinfectant.

Pharmacokinetics

At a dose of 50 mg/kg, benzoic acid was excreted by rodents, the rabbit, the cat and the capuchin monkey almost entirely as hippuric acid (95-100% at 24 hour excretion). In man at a dose of 1 mg/kg and the rhesus monkey at 20 mg/kg benzoic acid was excreted entirely as hippuric acid.

Toxicological Studies

The applicant has provided satisfactory data in support of the toxicology of benzyl alcohol and cross referred to the data submitted in support of the original application for PropoFlo10 mg/ml Emulsion for Injection for Dogs and Cats. This is considered acceptable.

A study was performed to check the toxicity of benzyl alcohol following single intravenous administration. The results indicated that LD^{2}_{50} when administered intravenously to cat was greater than 80 mg/kg. The LD_{50} by the subcutaneous route was greater than 1372 mg/kg in the cat. A single dose study was also conducted in dogs which showed LD_{50} to be 830-1060 mg/kg when benzyl alcohol was administered intravenously.

Repeated dose toxicity studies were conducted in mice and rats. A NOEL[3] of 500 mg/kg/day in females and 250 mg/kg/day in males in a 16 day and 200 mg/kg/day for both sexes in a 13 week oral toxicity study, was established.

A NOEL of 125 mg/kg/day in females and 250 mg/kg/day in males in a 16 day and 400 mg/kg/day in both sexes in a 13 week oral toxicity study was reported in rats.

Other Studies

Reproductive Toxicity

References were provided which reported on three studies. In one study in mice, an oral dose of 550 mg/kg/day benzyl alcohol was administered at day 6 of gestation. No adverse effects were seen on the parameters examined, and the NOEL was 550 mg/kg/day. In a second study, also in mice, benzyl alcohol given at day 7 of gestation at 750 mg/kg/day, maternal toxicity effects were noted but effects were not see in the offspring. A NOEL was not determined.

Mutagenicity

A series of references were presented for mutagenicity studies in bacteria and rodents. In studies with *Bacillus subtilis*, mixed results were found between different authors using equivalent dose levels of benzyl alcohol, but negative results were seen with *Salmonella typhimurium* and *Escherichia coli*. Benzyl alcohol was generally negative in mouse and rat genotoxicity assays, with any adverse effects seen only at high doses. Benzyl alcohol was not mutagenic in an in vivo micronucleus test in which mice were given up to 200 mg/kg bw by intraperitoneal injection, nor in mouse or rat replicative DNA synthesis assays in which benzyl alcohol was administered orally.

[2] Median Lethal Dose.
[3] No Observed Effect Level.

Carcinogenicity

No evidence for carcinogenicity was seen in reference data submitted.

Observations in Humans

The applicant provided bibliographical data which showed that some evidence was observed for skin irritation and sensitisation. The SPC carries a suitable warning.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:-

- Use aseptic techniques when administering the product.
- People with known hypersensitivity to any of the ingredients should avoid contact with the veterinary medicinal product.
- This veterinary medicinal product is a potent drug, exercise caution to avoid accidental self-injection. Preferably use a guarded needle until the moment of injection.
- In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.
- Advice to the doctor: do not leave the patient unattended. Maintain airways and give symptomatic and supportive treatment.
- In case of splashes on the skin or in the eyes, wash off immediately.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was required. The assessment concluded that as the product will be used infrequently and given to individual animals in a controlled environment, by a veterinary professional, the risk posed to the environment is therefore negligible.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Propofol (2,6-diisopropylphenol) is an intravenous sedative hypnotic agent for use in the induction and maintenance of general anaesthesia.
Propofol is a short-acting anaesthetic characterised by rapid onset and short duration of anaesthesia and by rapid recovery. Propofol produces unconsciousness by its depressant action on the central nervous system.

Pharmacokinetics

Intravenous injection is followed by extensive metabolism of propofol in the liver to inactive conjugates which are excreted in the urine (major route) and faeces. Elimination from the central compartment occurs rapidly, with an initial half-life of less than 10 minutes. After this initial phase, the decrease in plasma concentration is slower.

Tolerance in the Target Species of Animals

The applicant submitted two preliminary non GLP cat safety studies and two pivotal GLP repeat dose studies.

A GLP-compliant tolerance study was conducted in beagle dogs following an intravenous dose administration to assess the potential toxicity of PropoFlo 1% (Multidose) (preserved formulation of PropoFlo) by comparing its effects induced post IV administration at clinical and exaggerated dose levels with the effects induced post IV administration of 2 controls. This study provided evidence for the clinical efficacy of PropoFlo 1 % (Multidose) at low and high doses. PropoFlo 1 % (Multidose), when given at 1xRTD[4] for induction, caused a shorter duration and recovery period and less cardiorespiratory depression when the same parameters were compared to those seen at 3xRTD. The study also provided evidence for the tolerance of the addition of benzyl alcohol as a preservative at a concentration of 2 % when the preserved propofol emulsion is used at 3xRTD for induction. The applicant also provided supportive study to determine the toxicity of 2% benzyl alcohol in healthy beagle dogs when given by a single intravenous infusion. A suitable number of dogs were divided into different group. The test product was administered as a single intravenous loading dose followed by an intravenous infusion via a disposable catheter inserted into a cephalic vein connected to an infusion pump. All animals were subjected to clinical monitoring during the treatment and then daily for seven days. No mortalities or body weight changes occurred during the study.

A non-GLP study was conducted to evaluate the toxicity of MultiDose PropoFlo in cats when compared with data using Rapinovet at high doses in cats. A

[4] Recommended Treatment Dose

suitable number of cats were divided into different group. The study concluded that the clinical effects of Rapinovet and Multidose PropoFlo were similar when administered at 2.44xRTD and at 1.65xRTD for induction with 6 incremental doses at 4.4xRTD for maintenance. Hypothermia, apnoea and bradycardia were the most common side effects.

Another study was conducted to evaluate the toxicity potential of 3 different strengths of benzyl alcohol emulsion in healthy domestic short-hair (DSH) cats following a single IV administration. A suitable number of cats were divided into different groups. All animals were subjected to physical examination and clinical monitoring. No clinical signs or clinically significant changes in physiological parameters were observed following 2 % benzyl alcohol infusion. Two cats showed transient and minor signs of toxicity following 4% benzyl alcohol infusion. Therefore, it was concluded that the 2 % benzyl alcohol emulsion has an appropriate 2-fold margin of safety.

Another study was conducted to evaluate the toxicity of propofol containing 2 % benzyl alcohol as a preservative in domestic cats, post IV administration, both as a single injection and when used to maintain a prolonged anaesthesia. The study was conducted in accordance with the principles of GLP. A suitable number of cats were divided into different groups. All animals were subjected to clinical monitoring, neurological examinations, adverse reactions, body weight and food consumption. No mortalities occurred during the study. The study concluded that there were no remarkable differences for any parameter examined between administration of either PropoFlo MultiDose or PropoFlo following IV administration, both as a single injection (8.0 mg/kg) and when used to maintain a prolonged anaesthesia (24.0 mg/kg) in cats. In particular, there was no notable consistent difference in duration of anaesthesia and quality of recovery. There were no test article-related effects on physiological or neurological parameters during anaesthesia. Thus, there was no evidence of toxicity due to the presence of benzyl alcohol in the PropoFlo MultiDose preparation.

IV.B Clinical Studies

Clinical Efficacy

A bioequivalence study was conducted for the original generic Marketing Authorisation application (National Application), for PropoFlo, 10 mg/ml Emulsion for Injection for Dogs and Cats to confirm the “essential similarity” between the unpreserved single-dose product PropoFlo and the original reference product Rapinovet 10 mg/ml Emulsion for Injection. Propofol is virtually insoluble in water and both PropoFlo and Rapinovet are formulated in the same oil-in-water emulsion. The bioequivalence study was conducted in beagles, as dogs were considered to be the major target species, to confirm that there was no difference in bioavailability between PropoFlo and Rapinovet as a result of possible differences in the physical properties of the emulsions i.e. globule size and distribution.

Laboratory Trials

Data were not required for this section.

Dose confirmation studies

Data were not required for this section.

Field Trials

Data were not required for this section.

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 for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

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.

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