Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Propodine 10 mg/ml Emulsion for Injection/Infusion for Dogs and Cats

Date Created: June 2019

MODULE 1

PROPOSED PRODUCT SUMMARY

EU Procedure number	UK/V/0679/001/DC
Name, strength and pharmaceutical form	Propodine 10 mg/ml Emulsion for Injection/Infusion for Dogs and Cats, Emulsion for injection
Applicant	Le Vet Beheer B.V., Wilgenweg 7 3421 TV Oudewater The Netherlands
Active substance(s)	Propofol
ATC Vetcode	QN01AX10
Target species	Cats, Dogs
Indication for use	– General anaesthesia for diagnostic or surgical procedures of short duration, lasting up to five minutes. – Induction and maintenance of general anaesthesia. – Induction of general anaesthesia where maintenance is provided by inhalation anaesthetic agents.

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	Well established use/bibliographic application in accordance with Article 13 (a) of Directive 2001/82/EC as amended.
Date of conclusion of the decentralised procedure	13th March 2019
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden

I. SCIENTIFIC OVERVIEW

This application is for an emulsion for injection/infusion for dogs and cats, Propodine 10 mg/ml Emulsion for Injection for Dogs and Cats, containing 10 mg/ml propofol as the active substance. The product is used for general anaesthesia for diagnostic or surgical procedures of short duration, lasting up to five minutes, for the induction and maintenance of general anaesthesia, and for the induction of general anaesthesia where maintenance is provided by inhalation anaesthetic agents. The dose rate is variation depending on the species, patient response and required drug interactions. Refer to the Summary of Product Characteristics (SPC) for full details.

This was an application in accordance with Article 13 (a), (well established use/bibliographic application) of Directive 2001/82/EC, as amended. The active substance, propofol, has had well established veterinary use for at least ten years, with recognised efficacy and an acceptable level of safety. The first propofol-containing veterinary medicinal product, Rapinovet 10 mg/ml Emulsion for Injection was authorised in the UK in 1987 and has been reviewed. It was expired on 20 March 2013.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto 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. 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 [1] 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 CONSTIUENTS

II.A. Composition

The product contains 10 mg/ml propofol and the excipients egg phospholipids for injection, glycerol, soya-bean oil refined, sodium hydroxide (for pH adjustment), water for injections and nitrogen.

The container/closure system consists of colourless type I glass vials of 20 ml, 50 ml and 100 ml closed with a coated bromobutyl rubber stopper and aluminium cap in a carton box. The particulars of the containers and the 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.

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 the preparation of the aqueous phase, preparation of the oil phase, homogenisation to prepare the emulsion, transfer to the filling vessel, filling of vials and terminal sterilisation.

II.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.

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 comply with Ph. Eur monographs. All Certificates of Analysis were provided as appropriate. All packaging materials complied with specifications.

[1] Efficacy – The production of a desired or intended result.

II.C.4. Substances of Biological Origin

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

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 description, extractable volume, pH, fatty acid content, globule size, identity of active substance and degradation products, particulate analysis, sterility and the presence of endotoxins.

II.F. Stability

Stability data on the active substance and finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance 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.
- Do not freeze.
- Store in the outer carton in order to protect from light.
- Withdrawn product should be used immediately. Product remaining in the vial should be discarded.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Bibliographical data has been provided.

Pharmacodynamics

Propofol is a general anaesthetic characterised by rapid onset and short duration of anaesthesia. Recovery from anaesthesia is usually rapid.
Propofol primarily acts by enhancing the inhibitory synaptic neurotransmission mediated by GABA (gamma-aminobutyric acid) through binding to the GABA type A ($GABA_A$) receptor. However, the glutaminergic and noradrenergic neurotransmitter systems are also thought to have a role in mediating the effects of propofol.

Pharmacokinetics

After intravenous injection, blood concentrations of propofol demonstrate a rapid distribution phase, followed by elimination of drug from the body and a slower redistribution phase. This first phase, with a distribution half-life of approximately 10 min is clinically relevant, since recovery from anaesthesia occurs subsequent to the redistribution of propofol from the brain. In dogs, no accumulation of blood levels has been observed after repeated daily dosing. Generally, clearance is higher in dogs than in cats, although breed differences exist in dogs. In dogs, clearance is higher than hepatic blood flow, however, clearance is reduced during prolonged infusion (4h), most likely caused by a reduction in hepatic blood flow. The volume of distribution is high in both dogs and cats. Propofol is highly bound to plasma protein (96-98%). Clearance of the drug occurs through hepatic metabolism followed by renal elimination. A small amount is excreted in the faeces. Drug accumulation has not been evaluated in cats. However, based on available pharmacokinetic data, it is likely that drug accumulation occurs in this species upon repeated daily dosing.

Toxicological Studies

The applicant provided bibliographical data.

- Single Dose Toxicity

Relevant published studies were submitted. Of note, four studies provided data on the LD_{50}[2] relevant for mice and rats. Over three studies, an LD_{50} of between 40.45 mg/kg and 62.2 mg/kg were noted. In one rat study, an LD_{50} of 30.3 mg/kg was noted.

- Repeated Dose Toxicity

A number of studies were presented which described repeat dose toxicity studies relevant for humans. The applicant has compared an appropriate worst-case exposure of 0.15 mg/kg (intramuscular injection) to a LOEL[3] (in the absence of NOEL[4]), of 0.3 mg/kg (intravenous injection), resulting in an MOE of 2. Based on the information provided by the applicant, a safety factor of 10 can

[2] LD_{50} -
[3] LOEL- Lowest observed effect level.
[4] NOEL - No observed effect level.

be accepted for use in the quantitative user risk assessment. Therefore, a risk to the user cannot be ruled out and suitable user safety warnings were added to the SPC and product literature.

- Reproductive Toxicity, including Teratogenicity:

Satisfactory data citing that a single dose of propofol 0.15 mg/kg bodyweight is unlikely to adversely affect a foetus was submitted. Suitable warnings appear on the SPC and product literature.

- Mutagenicity

Studies supported the premise that propofol is not mutagenic.

- Carcinogenicity

Studies submitted showed that propofol is not a carcinogen.

Studies of Other Effects

The applicant has provided bibliographical data to support the premise that propofol is partially irritant to skin and eyes. Evidence was also found which showed hypersensitivity reactions to the active substance, and neurotoxicity reactions are a risk for foetuses and infants. The SPC and product literature carries suitable warnings.

Observations in Humans

References were provided. The SPC and product literature carries suitable warnings.

Studies on Metabolites, Impurities, Other Substances and Formulation

The product contains egg phospholipid, glycerol, soybean oil, sodium hydroxide, and water for injection. These excipients have well-established use in many other authorised veterinary medicinal products. The excipients are generally of low toxicological concern. With regards to soybean oil and egg phospholipid, there remains a potential for these excipients to elicit hypersensitivity-type reactions in sensitised individuals.

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:

- Propofol is a potent drug: particular care should be taken to avoid accidental self-administration. A guarded needle should preferably be used 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, but DO NOT DRIVE as sedation may occur.
- Avoid contact with the skin and eyes as this product can cause irritation. Wash off splashes from the skin and eyes immediately with plenty of water. Seek medical advice if irritation persists.
- This product may cause hypersensitivity (allergy) reactions in those that are already sensitised to propofol or other drugs, soya or egg. People with known hypersensitivity to these substances should avoid contact with the veterinary medicinal product.
- Advice to the doctor: Do not leave the patient unattended. Maintain airways and give symptomatic and supportive treatment.

Environmental Safety

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

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 provided bibliographical data describing the pharmacodynamic and pharmacokinetic properties of the active substance, as described in Section III, Safety and Residues Documentation.

Tolerance in the Target Species

The applicant provided numerous references. The SPC and product literature carry extensive warnings and instructions regarding use and dose. Key points include avoiding use of the product in hypersensitive animals regarding the active substance and excipients, the exercise of caution when using the product in clinically compromised animals, the use of supplementary analgesic agents when necessary and care when using the product in young animals. The safety of the product has not been established in dogs or cats younger than 4 months and should be used in these animals only according to the risk/benefit assessment by the responsible veterinarian. Refer to the SPC and product literature for further guidance, dosage and drug interaction details.

IV.II. Clinical Documentation

As this was a full bibliographical application, the applicant submitted a large number of references to support authorisation of the product. Full justification was provided for all aspects of use of the product. The product is used according to the risk/benefit of the responsible veterinarian, and in accordance with guidance and data provided in the SPC and product literature.

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.

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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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