United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Proposure 10 mg/ml Emulsion for Injection for Dogs and Cats

Date Created: February 2017

PuAR correct as of 05/12/2018 when RMS was transferred to FR.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0573/001/DC
Name, strength and pharmaceutical form	Proposure 10 mg/ml Emulsion for Injections for Dogs and Cats
Applicant	Merial
Active substance(s)	Propofol
ATC Vetcode	QN01AX10
Target species	Dogs and Cats
Indication for use	A short-acting, intravenous general anaesthetic with a short recovery period. Intended for brief procedures lasting up to five minutes. For induction and maintenance of general anaesthesia by administration of incremental doses to effect. For 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	Bibliographic application in accordance with Article 13 (a) of Directive 2001/82/EC as amended.
Date of conclusion of the decentralised procedure	23rd November 2016
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Luxembourg, The Netherlands, Norway, Poland, Romania, Slovakia, Spain, Sweden

I. SCIENTIFIC OVERVIEW

This was an application for a marketing authorisation for Proposure 10 mg/ml emulsion for injection for dogs and cats, submitted as a bibliographic application under Article 13 (a) of Directive 2001/82/EC, as amended, (well-established veterinary use). The majority of the data cited by the applicant related to Rapinovet 10 mg/ml Emulsion for Injection for Infusion, an expired veterinary medicinal product, or Diprovan 10 mg/ml Emulsion for Injection or Infusion, authorised for human use. The proposed product is indicated as a short-acting, intravenous anaesthetic with a short recovery period, for dogs and cats, and is intended for brief procedures lasting up to five minutes. It is also indicated for the induction and maintenance of general anaesthesia by administration of incremental doses to effect. Also, it is for the induction of general anaesthesia where maintenance is provided by inhalation anaesthetics.

Refer to the SPC for specific detail on amounts to be administered and administration route, and for specific information with regard to induction and maintenance of anaesthesia. Dose can vary between animals, and in particular, the use of pre-anaesthetic drugs may significantly reduce propofol requirements depending on the type of dose of pre-anaesthetic drug used. Actual dose requirements for individual animals may be significantly lower or higher that the average dose.

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.[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 CONSTIUENTS

II.A. Composition

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

The container/closure system consists of colourless Type I glass vials, closed with a siliconised bromobutyl rubber stopper and an aluminium cap. 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.

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 mixing and stirring processes, followed by filtration and autoclaving, and subsequent filling of the products into vials.

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 propofol, an established active substance described in the European Pharmacopoeia/British Veterinary Pharmacopoeia and has a valid CEP. 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.

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

All excipients and containers comply with relevant pharmacopoeial standards.

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. The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

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 include those for: description, extractable volume, pH, free-fatty acids content, mean droplet diameter, identity of the active substance, degradation products, lysophosphatidylcholine, contamination, sterility and bacterial endotoxins.

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. The retest period is 36 months when stored under nitrogen in aluminium bottles coated with an epoxy phenolic resin and closed with a polypropylene screw cap with Teflon liner.

A stability study has been conducted for 6 batches of the finished product. Three were stored in 20 ml vials, two in 50 ml vials and one was stored in 100 ml vials. The vials were stored inverted, with the exception of the samples used for appearance testing, which were stored vertically. Samples were stored for up to 36 months at 30°C/75%RH and 5ºC (no humidity control) and up to 6 months at 40ºC/75%RH.

All variables measured were within acceptable parameters.

G. Other Information

- Shelf life of the veterinary medicinal product as packaged for sale: 2 years.

- Shelf life after first opening the immediate packaging: immediate use.

- Do not freeze.
- Withdrawn product should be used immediately. Product remaining in the container should be discarded.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Bibliographical data has been provided.

Pharmacodynamics

The applicant submitted data with regard to use of the active substance in man. Propofol is believed to interact with specific structures on the post-synaptic membrane, resulting in a decreased dissociation of γ-aminobutyric acid (GABA) from receptors located in the central nervous system (CNS). $GABA_A$ receptors are predominantly associated with propofol activity, with some effect occurring via glutaminergic and noradrenergic receptors. Primary pharmacodynamic effects in man are rapid onset of hypnosis after administration of 2 – 2.5 mg/kg. Median effective dose (ED_{50}) for loss of consciousness is 1 – 1.5 mg/kg. Duration of hypnosis is dose-dependent and is sustained 5 – 10 minutes after a 2 – 2.5 mg/kg dose. The induction dose is affected by age, which decreases with age. Sub-hypnotic doses may result in amnesia and sedation.

Clinical uses in humans are induction and maintenance of anaesthesia, (induction dose is generally 1 – 2.5 mg/kg in most adults under 55 years of age, maintenance dose is approximately 4 – 12 mg/kg/hour). Sedation, (initially 6 – 9 mg/kg/hour for 3 – 5 minutes and 1.5 – 4.5 mg/kg/hour for maintenance. Propofol has also been used as an antiemetic and anti-pruritic. Sub-hypnotic doses administered 10 -15 mg can be administered to treat post-operative nausea and vomiting. Results with regard to anti-pruritic action were conflicting.

Propofol has secondary pharmacodynamic effects on respiration, the cardiovascular system and the motor system.

The active substance is a respiratory depressant. Maintenance infusion at 100 µg/kg/min results in a 40% decrease in tidal volume with a 20% increase in respiratory frequency. A 25 – 30% chance of developing apnoea is possible at induction.

The effects of Propofol on the cardiovascular system include hypotension and bradycardia. Hypotension may occur when propofol is administered rapidly, and in the elderly. An induction dose of 2 – 2.5mg/kg my induce a 24 – 40% reduction in systolic blood pressure. Reset or inhibition of the baroreflex may

induce a tachycardic response to hypotension, causing a drop in cardiac output and heart rate. Special care must be taken with patients taking negative chronotropic medicines and in persons at the extremes of age. Effects are generally dose-dependent.

Effects on the motor system include dystonic movement myoclonus, and choreathetosis. The active has a positive effect on drug-induced seizures. Side-effects include fever, nausea, vomiting and headache. Propofol infusion syndrome is rare, but lethal syndrome has been associate4d with administration of propofol at ≥ 4 mg/kg/hour for 48 hours or longer in children and critically ill adults.

Pharmacokinetics

Propofol is rapidly and extensively metabolised in man and in animals, with 88% of the dose being excreted in the urine as conjugates. Metabolism is predominantly performed in the liver, with water-soluble compounds excreted via the kidneys. Less than1% is excreted unchanged in urine and 2% in faeces. Extra-hepatic elimination has been proposed for propofol, as clearance of the active substance exceeds hepatic blood flow. It is suggested that the lungs and kidney play a role in extra-hepatic metabolism. Propofol is extensively and rapidly distributed throughout the body tissues. In rats, the highest level of propofol was observed in the liver. Recovery after administration is rapid due to the high clearance level of the active substance. Propofol readily crosses the placenta, and is also expressed in breast milk after crossing the placental barrier.

Toxicological Studies

The applicant has provided bibliographical data

- Single Dose Toxicity

In mice, single dose toxicity tests yielded LD_{50}[3] values of 57.9 and 21.4 mg/kg bw. Doses of 12.85 and 11.6 mg/kg bw were the median HD_{50}[4] dose. In a study in rats investigating whether non-sedating doses of propofol caused a discriminative stimulus, death occurred in 8/32 animals at doses of 5 and 10 mg/kg bw.

- Repeated Dose Toxicity

A study investigating organ toxicity and mortality in relation to propofol sedation at large doses was performed in artificially ventilated rabbits. Dose was

[3] LD_{50} – Median lethal dose at which 50% of a tested population are terminated.
[4] HD50 – Median Hypnotic dose at which righting reflexes are abolished for 30 seconds in 50% of a tested population.

administered at a rate of 20 mg/kg/hour and increase up 65.7 mg/kg/h in 5 mg/kg/hour increments. All animals were deceased 26 – 38 hours after commencement of the test. Signs of deterioration were noted after 21 ± 3.2 hours of infusion and included acidosis and diminished capillary oxygen saturation, followed by low cardiac output and pulmonary oedema. It was noted that fatal multi-organ dysfunction occurred No NOEL was reported.

- Embryotoxicity/foetotoxicity (including teratogenicity)

No evidence of adverse foetal effects was noted in rats and rabbits in submitted studies, at doses of 5 – 15 mg/kg/day. Extensive literature available from human observations satisfactorily shows that propofol is not a teratogen at therapeutic doses in humans.

- Mutagenicity

Data showed that propofol is not mutagenic.

- Carcinogenicity

Propofol is not considered to be a carcinogen.

Studies of Other Effects

The applicant has provided bibliographical data. Local effects consist of the potential to irritate eyes, skin and mucous membranes, while the most common effect is pain on injection. There is some evidence of hypersensitivity to either propofol or the excipients. The product should not be used in cases of known hypersensitivity to either the active substance or the excipients. See the SPC for full detail.

Observations in Humans

Bibliographical data were provided. Adverse effects may affect the following systems: cardiovascular, respiratory and nervous systems. Psychological and psychiatric issues may occur. Hyperlipidaemia or hypertriglyceridemia may occur, propofol infusion syndrome may occur. Adverse liver effects may be seen, incidences of pancreatitis have been noted, in addition to instances of rhabdomyolysis. Aberration has also been noted in sexual function. Propofol has also been recognised to have reward potential.

Studies on metabolites, impurities, other substances and formulation

The product contains egg phosphatide, glycerol, soybean oil, sodium hydroxide, nitrogen and water for injection. These excipients have well-established use in many other veterinary medicinal products authorised in the EU. The excipients are generally of low toxicological concern and, at the levels seen in the test product, are regarded as a non-irritant. There is a potential for soybean oil to elicit hypersensitivity type reactions in sensitised individuals.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that when used as advised in the SPC, the risk to the user are low.

Suitable discussion was provided on skin exposure and accidental ingestion, with mitigating processes also described. The active substance has long been used in human medicine, providing rapid onset of effect and recovery.

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, with suitable additions are appropriate:

- Propofol is a potent general anaesthetic drug and particular care should be taken to avoid accidental self-injection. 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 to the physician.
- People with known hypersensitivity to propofol or any of the excipients should avoid contact with the veterinary medicinal product.
- Avoid contact with the skin and eyes as this product can cause irritation.
- Wash splashes from skin or eyes immediately with plenty of fresh water. Seek medical advice if irritation persists.
- **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.

Phase I:

The product will only be used in non-food animals and as a result environmental exposure will be low. The vast majority of the dose will be metabolised and

excreta containing residues of the product will be eliminated in the recovery area and probably incinerated. A Phase II ERA was not required.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics in the target species

The applicant submitted a significant amount of bibliographical data sufficient to demonstrate the safety of the product in relation to the target species when used as directed in the SPC. The mechanism of action was sufficiently described. It was noted in particular that recovery in cats may be prolonged subsequent to propofol infusion. The SPC carries suitable information at section 5.1.

Secondary pharmacodynamic effects

The applicant provided data which described the secondary pharmacodynamic effects of propofol. However, the use of the product in this instance is specified in the SPC as being for use as an anaesthetic only. The risk of apnoea is discussed in the SPC in sections 4.5 (i), 4.6 and 4.10. Isection 4.5 of the SPC, specific reference is made to the requirement to note that the clearance of propofol in dogs over 8 years of age is slower than in younger animals. A lower dose of propofol may need to be considered.

Pharmacokinetics in the target species

The pharmacokinetic properties of propofol have been sufficiently described in bibliographical data for each target species. Section 5.2 of the SPC carries relevant data.

Interaction with other medicinal products/overdose/ incompatibilities

Sections 4.8, 4.10 and 6.2 of the SPC carry specific information related to drug interactions with other medicinal products, incompatibilities with other veterinary medicinal products and action to be taken in the case of overdose.

Tolerance in the Target Species

The applicant provided a significant amount of bibliographical data which showed that as described in sections 4.6 and 4.10 of the SPC, the product is considered to be relatively safe for the target species when used as directed. The product must not be used in animals with known hypersensitivity to the active substance or any excipients. With regard to pregnancy in the target species, the SPC states that the safety of this product in foetuses/neonates and during lactation has not been established.

Successful use of the product in dogs for induction prior to Caesarean section has been reported. Only use according to the benefit-risk assessment by the responsible veterinarian.

IV.II. Clinical Documentation

Laboratory Trials

The applicant provided acceptable bibliographical data describing dose determination studies in both species. Based on these data, section 4.9 of the SPC contains detailed information on the induction and maintenance of anaesthesia in both species.

Field Trials

A substantial number of references were submitted as clinical documentation, many of which also applicable for the discussion of dose determination. Evidence was presented from field trials confirming that the use of propofol in dogs and cats is relatively safe when used as described in the SPC.

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.

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