Bundesamt für Verbraucherschutz und Lebensmittelsicherheit

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Mauerstraße 39-42
10117 Berlin
(Germany)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Vetofol 10mg/ml Emulsion for Injection for cats and dogs
(AT, CY, EE, DE, EL, LV, PT, ES)

Vetofol vet 10mg/ml Emulsion for Injection for cats and dogs
(FI)

Norofol 10mg/ml Emulsion for Injection for cats and dogs
(UK, BG, CZ, LT, RO, SI, SK)

Date: 11 October 2018

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0317/001/MR
Name, strength and pharmaceutical form	Vetofol 10 mg/ml emulsion for injection for cats and dogs (DE, AT, CY, EE, EL, ES, LV, PT) Vetofol vet 10 mg/ml emulsion for injection for cats and dogs (FI) Norofol 10 mg/ml emulsion for injection for cats and dogs (BG, CZ, LT, RO, SI, SK, UK)
Applicant	Norbrook Laboratories Ltd. Station Works, 11 Camlough Road BT35 6JP Newry, Co. Down Northern Ireland
Active substance(s)	Propofol
ATC Vetcode	QN01AX10
Target species	Cats, Dogs
Indication for use	Vetofol Injection is indicated for use in dogs and cats as a short-acting, intravenous general anaesthetic for procedures of short duration, lasting up to 5 minutes; for the induction and maintenance of general anaesthesia using incremental doses to effect; for the induction of general anaesthesia where maintenance is provided by inhalation anaesthetics.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicinal Agencies website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 32 (2) of Directive 2001/82/EC, as amended by 2004/28/EC.
Date of completion of the original mutual recognition procedure	29 September 2010
Date product first authorised in the Reference Member State UK (MRP only)	09 January 2009
Concerned Member States for original procedure	AT, BG, CY, CZ, EE, ES, FI, GR, LT, LV, PT, RO, SI, SK, UK (former RMS)

I. SCIENTIFIC OVERVIEW

Norofol 10 mg/ml emulsion for injection for cats and dogs is authorised for use in dogs and cats as a short-acting, intravenous general anaesthetic for procedures of short duration, lasting up to 5 minutes. The product is also indicated for the induction and maintenance of general anaesthesia using incremental doses to effect; and for the induction of general anaesthesia where maintenance is provided by inhalation anaesthetics. The product is indicated for intravenous administration and contains propofol as an active substance. The product is packaged in a cardboard box containing one clear glass (type I) vial of 20 ml or one clear glass (type I) vial of 50 ml. The vials are closed with bromobutyl bungs and aluminium caps. The dose rate is 4.0 - 6.5 mg/kg bodyweight for dogs and 6.0 - 8.0 mg/kg bodyweight for cats.

This application for the mutual recognition of a UK marketing authorisation was submitted in accordance with Article 32 (2) of Directive 2001/82/EC, as amended by 2004/28/EC. The product was authorised in the UK on 9th January 2009. Bioequivalence is claimed with the reference product Rapinovet 10 mg/ml emulsion for injection, which has been approved in the UK since 1987.

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; the slight reactions observed are indicated in the SPC[1]. The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as

[1] Summary of Product Characteristics

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

A. Composition

The product contains the active substance propofol and excipients lecithin, glycerol, refined soybean oil, sodium hydroxide and water for injections.

The product is packaged in a cardboard box containing one clear glass (type I) vial of 20 ml or one clear glass (type I) vial of 50 ml. The vials are closed with bromobutyl bungs and aluminium caps. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and lack of presence of a preservative have been justified.

The product is an established pharmaceutical form and its development has been 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, propofol, is an established active substance and supporting data have been provided in the form of a Certificate of Suitability. It is considered that the manufacturing process is adequately controlled and the active substance specifications have been suitably justified.

All excipients, with the exception of lecithin, are the subject of monographs in the European Pharmacopoeia. Nitrogen meets the requirements of the current European Pharmacopoeia monographs for Nitrogen and Nitrogen, Low Oxygen. Lecithin does not appear in the European Pharmacopoeia or the Pharmacopoeia of a member state. It is the subject of a food additive monograph (E322) and a draft monograph for the United States Pharmacopoeia (USP). The supplier's specification is comprehensive, includes the important elements of both of these monographs and is considered to give a very good level of control.

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

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

E. Control on intermediate products

There are no intermediate products.

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.

G. Stability

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 period of two years is justified.

Finished product:

Data have been provided which indicate that the finished product is stable for 2 years when stored at a temperature below 25° C.
Withdrawn product should be used immediately.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- This product does not contain an antimicrobial preservative.

Special precautions for storage:

- Do not store above 25°C.

- Do not freeze.
- Protect from light.
- Keep the container in the outer carton.
- Store vials in the upright position.

Shelf-life:

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

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

This application for the mutual recognition of a UK marketing authorisation was submitted in accordance with Article 32 (2) of Directive 2001/82/EC, as amended by 2004/28/EC, and bioequivalence with the reference product, Rapinovet 10 mg/ml emulsion for injection, has been demonstrated. Therefore, results of pharmacological, toxicological and clinical trials are not required.

User Safety

The following precautions are listed on the SPC and product literature:

- This 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.
- Wash off splashes from the skin and eyes immediately.
- In the event of accidental self-administration, seek urgent medical attention and show the label to the physician. **Advice to Doctor:** Do not leave the patient unattended. Maintain airways and give symptomatic and supportive treatment.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in accordance with VICH[2] guideline which showed that no further assessment is required. 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)

[2] International Co-operation on Harmonisation of Technical Requirements for Registration of Veterinary Products

This application for the mutual recognition of a UK marketing authorisation was submitted in accordance with Article 32 (2) of Directive 2001/82/EC, as amended by 2004/28/EC, and bioequivalence with the reference product, has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics:
Propofol (2,6 di-isopropylphenol, Diprivan; ICI 35868) is a nonbarbiturate substituted isopropyl phenol which is used for the induction and maintenance of anesthesia. Propofol is a short-acting, intravenous general anaesthetic for procedures of short duration, lasting up to 5 minutes. Recovery from anaesthesia is usually rapid.

Pharmacokinetics:
The application was based on essential similarity of Norofol 10 mg/ml emulsion for injection for cats and dogs to the established product Rapinovet 10 mg/ml emulsion for injection. The applicant demonstrated that the products were essentially similar by submitting the report of a bioequivalence study.

The study utilised a well-accepted design known as a “crossover” design, and was conducted to GLP[3] standards. The study involved two groups of dogs. The first group received a single intravenous (i/v) injection of 6.5 mg/kg propofol of either Norofol 10 mg/ml emulsion for injection for cats and dogs or Rapinovet 10 mg/ml emulsion for injection over a period of 60 seconds. After a 14 day wash-out period; dogs received the alternative treatment at the same dose rates. Blood samples were collected from all the dogs at intervals throughout the study and the amount of propofol in these samples was measured using a validated method. AUC[4] was used to demonstrate bioequivalence in accordance with the bioequivalence guidelines. Confidence intervals from Cmax[5] and AUC were within the stipulated range of 80-125%, bioequivalence was therefore established.

Tolerance in the Target Species of Animals

Since the application was made in accordance with Article 32 (2) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of bioequivalence new tolerance data was not required as it has already been presented for the reference product.

IV.B Clinical Studies

[3] Good laboratory practice
[4] Area under the curve
[5] Maximum plasma concentration

As the application was made on the basis of essential similarity with an established product marketed in the EU for at least 10 years, and bioequivalence has been demonstrated with the reference product, results of toxicological or pharmacological tests and clinical trials were not required. However, the applicant conducted a study to compare the anaesthetic and cardiorespiratory effect of propofol (2,6 Di-Isopropylphenol) in dogs following administration of Norofol 10 mg/ml emulsion for injection for cats and dogs and Rapinovet 10 mg/ml emulsion for injection. This study used a two treatment period cross over design with 4 dogs receiving Norofol 10 mg/ml emulsion for injection for cats and dogs and 4 dogs receiving Rapinovet 10 mg/ml emulsion for injection in period I with a washout period of 14 days before treatment reversal in period II. Each propofol formulation was administered at the recommended dose rate for induction of 6.5 mg/kg over a period of 40 seconds. Thereafter, incremental doses of 10% of the initial dose were administered until intubation was completed. Anaesthesia was then maintained for approximately 20 minutes using incremental doses of 2.5 mg/kg as required. Anaesthetic and cardiorespiratory parameters were monitored throughout the periods of anaesthesia and daily health monitoring conducted throughout the study. Animals were monitored for adverse effects throughout the study. The study concluded that Norofol 10 mg/ml emulsion for injection for cats and dogs is as efficacious as the reference product.

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 Heads of Veterinary Medicinal Agencies website (www.hma.eu).

This section 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.

•	28 March 2019	Change in manufacturer responsible for batch release in the EU from UK to Ireland.
•	11 October 2018	Change in RMS from UK to DE.
•	13 December 2016	Update of the test procedure to comply with the updated general Ph. Eur monograph.
•	04 February 2016	Addition of a new supplier of packaging materials
•	25 September 2014	Change of QPPV and update to the DDPS.
•	23 December 2013	Renewal procedure.
•	27 July 2013	Submission of an updated Ph. Eur. Certificate of Suitability.
•	15 March 2013	Addition of a supplier of packaging components.
•	18 February 2011	New MA – MRP.