College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Repose 500 mg/ml solution for injection injection (AT, BE, BG, CY, CZ, EL, ES, HR, HU, IE, IT, LU, PT, RO, SI, SK, UK)
Repose vet 500 mg/ml solution for injection (DK, FI, IS, NO, SE, EE, LT, LV, PL)
Repose solution for injection (FR)
Euthasol 500 mg/ml solution for injection (NL)

Date Created: May 2017

Updated: May 2019

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0320/001/DC
Name, strength and pharmaceutical form	Repose 500 mg/ml solution for injection
Applicant	Le Vet Beheer B.V. Wilgenweg 7 3421 TV Oudewater The Netherlands
Active substance	Pentobarbital sodium
ATC Vetcode	QN51AA01
Target species	Dogs, cats, rodents, rabbits, cattle, sheep, goats, pigs, horses and mink
Indication for use	Euthanasia

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Hybrid application in accordance with Article 13 (3) of Directive 2001/82/EC as amended
Date of conclusion of the decentralised procedure	29th March 2017
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom.

I. SCIENTIFIC OVERVIEW

This was an application for a generic 'hybrid' product, Repose, 500 mg/ml Solution for Injection, submitted under Article 13(3) of Directive 2001/82/EC, as amended. This was determined as a generic 'hybrid' application because the active substance contains a higher concentration of the active substance as compared to the reference product, Pentobarbital for Euthanasia 20% w/v Solution for Injection, marketed in the UK since August 1993. The proposed product contains 50% w/v pentobarbital sodium as opposed to 20% w/v for the reference product. The proposed product is intended for euthanasia ONLY, and is for use in dogs, cats, rodents, cattle, sheep, goats, pigs, horses and mink. The product must not be used for anaesthesia. Refer to the Summary of Product Characteristics (SPC) for advice on dose and route of administration to individual species.

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. Adequate measures should be taken to ensure that carcasses of animals treated with this product and the by-products of these animals do not enter the food chain and are not used for human or animal consumption.

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 500 mg pentobarbital sodium and the excipients ethanol (96 percent), Patent Blue V (E131), hydrochloric acid, dilute (for pH adjustment), sodium hydroxide, (for pH adjustment) and water for injections.

The container/closure system consists of Clear Type I glass vials containing 100 ml or 250 ml, and polypropylene vials containing 100 ml or 250 ml closed with a bromobutyl rubber stopper and aluminium cap in a carton box.

Carton box pack sizes:

1 or 12 vials of 100 ml.

1 or 12 vials of 250 ml.

The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation and the presence 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 a simple stirring and addition process of the ingredients, followed by packing, labelling and quarantine of the product. 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 pentobarbital sodium, an established active substance described in the European Pharmacopoeia (Ph. Eur), in accordance with an acceptable Certificate of Suitability. 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] Efficacy – The production of a desired or intended result.

All excipients apart from the colouring agent are are described in the Ph. Eur. Certificates of analysis were provided. The colouring agent, Patent Blue V, complies with the appropriate Regulation EC/231/2012 and is supported by a suitable certificate of analysis.

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 include those for: appearance, pH, relative density, refractive index, identification and assay of the active substance, related substances, volume and sterility.

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. A retest period of 60 months was acceptable for the active substance. Suitable results were provided in support of the shelf-life of the product as packaged for sale, and for the product in-use.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after opening of the immediate packaging: 56 days.
This veterinary medicinal product does not require any special storage conditions.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

As the key difference between the proposed product and the reference product is the concentration of the active substance, exemption from the requirement for bioequivalence studies in accordance with 7.1a of the Guideline on the Conduct of Bioequivalence Studies for Veterinary Medicinal Products (EMA/CVMP/016/00-Rev.2) was successfully claimed. (Refer to Section IV. Clinical Documentation for further information). Due to the nature of the application, no additional toxicological or pharmacological data were required.

Warnings and precautions as listed on the product literature are adequate to ensure safety of the product to users and the environment. Warnings with regard to user safety have been revised as compare to the reference product, in light of the increased concentration of the proposed product.

III.A Safety Documentation

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. The product is intended to be administered to animals only by veterinarians, accompanied by a veterinary assistant, (both being professionals). Therefore, the following applicant's user recommendations are appropriate:

- For use by a veterinary surgeon only.
- Pentobarbital is a potent hypnotic and a sedative, and thus potentially toxic in man. It can be absorbed systemically through the skin and if swallowed. Particular care should be taken to avoid accidental ingestion and self-injection. Only carry this product in an unarmed syringe to avoid accidental injection.
- Systemic uptake (including absorption via skin or eye) of pentobarbital causes sedation, sleep, CNS and respiratory depression. Moreover, this product may be irritating to the eye and can cause irritation to the skin as well as hypersensitivity reactions (due to the presence of pentobarbital). Embryotoxic effects cannot be excluded.
- Avoid direct contact with the skin and eyes, including hand-to-eye contact.
- This product is flammable. Keep away from sources of ignition.
- Do not smoke, eat or drink while handling the product.
- Avoid accidental self-injection or accidental injection of other persons when administering the product.
- People with known hypersensitivity to pentobarbital should avoid contact with the veterinary medicinal product.

- Handle the product with utmost care, especially pregnant and breastfeeding women. Wear protective gloves. This medicine should only be administered by veterinarians and should only be used in the presence of another professional that can assist in case of accidental exposure. Instruct the professional if not a medical professional about the risks of the product.
- Accidental spillage on the skin or in the eye must be washed off immediately with plenty of water. If there has been serious skin or eye contact or in the case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician. In the case of accidental ingestion, wash out mouth and obtain medical attention immediately. But DO NOT DRIVE as sedation may occur.
- After administration of this product, collapse will occur within 10 seconds. In case the animal is standing at time of administration, care should be taken by the person administering the veterinary medicinal product and any other persons present to keep a safe distance from the animal to avoid injury.

Environmental Safety

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

Phase I:

Given that the product will only be used by professionals in individual animals not intended for human consumption, the environmental risk assessment stops at Phase I.

The SPC and product literature contain the following information: The product is intended for euthanasia on the grounds of animal welfare to prevent (further) unnecessary suffering.

Any unused product must be disposed of in accordance with the Misuse of Drugs Regulations 2001.

Any waste material should be disposed of in accordance with national requirements.

III.B.2 Residues documentation

Not to be used in animals intended for human or animal consumption. Treated horses may never be slaughtered for human consumption. The horse must have been declared as not intended for human consumption under national horse legislation. There is no withdrawal period for such a product. Adequate measures should be taken to ensure that carcasses of animals treated with this product and the by-products of these animals do not enter the food chain and are not used for human or animal consumption.

IV. CLINICAL DOCUMENTATION

A waiver from bioequivalence studies was permitted under section 7.1(a) of the bioequivalence guideline. The guideline states a waiver is permissible if:

'The product is to be administered solely as an aqueous intravenous solution containing the same active substance as the currently approved product. However, if any excipients interact with the active substance (e.g. complex formation), or otherwise affect the disposition of the active substance, a bioequivalence study is required unless both products contain the same excipients in very similar quantity and it can be adequately justified that any difference in quantity does not affect the pharmacokinetics of the active substance.'

The proposed product is administered principally via the intravenous route. The intracardiac route, if required to be used, delivers the product directly to the bloodstream and is therefore comparable in this respect to the intravenous route. The speed of effect of the intraperitoneal route is comparable to the action of the reference product. The amount of product required is less than that of the reference product, and the excipients do not cause additional local tolerance issues. The SPC and product literature must be referred to for relevant advice on route of administration and special warnings for each target species.

Apart from a study to assess the syringeability of the proposed product as compared to reference product, no other clinical data were required. Results were acceptable.

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(s) 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 Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

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.

•	21 March 2019	Change in RMS