ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Euthasol vet. 400 mg/ml, solution for injection (AT, BE, EE, EL, FI, IE, IS, LT, LU, LV, NO, PL, SE, UK)

Euthasol 400 mg/ml, solution for injection (ES, PT)

Euthasol vet. Solution for injection (FR)

Euthasol vet. 400 mg/ml solution for injection for dogs, cats, rodents, rabbits, cattle, sheep, goats, horses and mink (IT).

UK/V/0370/001/DC

PuAR correct as of 25/03/2019 when RMS was transferred to IE. Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0370/001/DC
Name, strength and pharmaceutical form	Euthasol vet. 400 mg/ml, solution for injection
Applicant	LeVet B.V. Wilgenweg 7 3421 TV OudewaterThe Netherlands
Active substance(s)	Pentobarbital (as sodium salt)
ATC Vetcode	QN51AA01
Target species	Dogs, cats, rodents, rabbits, cattle, sheep, goats, horses, and mink
Indication for use	Euthanasia of domestic pets and smaller farm animals, mink and large animals.

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	Generic hybrid application in accordance with Article 13(3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	28th September 2011
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria, Belgium, Estonia, Finland, France, Greece, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Norway, Poland, Portugal, Spain, Sweden. Additional CMSs added for Repeat Use procedure: Denmark, Romania.

I. SCIENTIFIC OVERVIEW

This was a generic hybrid application for which the reference product was Pentobarbital for Euthanasia 20% Solution for Injection, authorised in the UK since August 1993. The product was deemed to be a generic hybrid application because it differs from the reference product in the quantity of active substance per ml.

Bioequivalence with the reference product was not demonstrated, but neither was the product ‘exempt’. It was agreed that due to the nature and intended use of the product and to avoid unnecessary use of experimental animals, the applicant’s justifications for omission of appropriate data was justified.

The indication for Euthasol vet. 400 mg/ml, solution for injection is for euthanasia in dogs, cats, rodents, rabbits, cattle, sheep, goats, horses and mink. The product is recommended to be administered at 140 mg per kg (0.35 ml/kg) in a single injection. The preferred method of administration is by intravenous injection. Adequate sedation can be applied first where necessary (mandatory for horses and cattle). Where intravenous injection is not possible, and only following deep sedation, the product may be administered via intracardiac injection, or following appropriate sedation via intraperitoneal injection (small animals only).

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.[1] 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 pentobarbital sodium and excipients benzyl alcohol (E1519), patent blue V (E131), ethanol (96%), propylene glycol and water for injections

The containers are colourless Type II glass vials with bromobutyl stoppers and aluminium closures, in 100 ml or 250 ml presentations. The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the presence of preservative is justified given the indication of the product. 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 manufacture consists of a simple mixing process to produce the solution followed by filtration, filling, and packing.

The patent blue is added to water and mixed at low speed. Separately, ethanol is added to water and mixed at high speed. Benzyl alcohol, pentobarbital sodium and propylene glycol are added to the ethanol and water solution and mixed at high speed. The solution is then sterilised by filtration and transferred into glass bottles.

Process validation data on two batches of the product have been presented in accordance with the relevant European guidelines.

[1] SPC – Summary of Product Characteristics.

C. Control of Starting Materials

The active substance is pentobarbital sodium, an established active substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice and in accordance with a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability. 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 are describes in the European Pharmacopoeia

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

A declaration has been provided stating that the finished product complies with the latest version of the Committee for Proprietary Medicinal Products (CPMP)/ Committee for Medicinal Products for Veterinary Use (CVMP) TSE guideline, confirming that no materials of animal origin are used to manufacture the product.

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 site have been provided demonstrating compliance with the specification. Tests include those for appearance, pH, identification of pentobarbital sodium, sterility and visible particles.

G. Stability

Stability data on 3 commercial-scale batches of 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. Tests include those for appearance, loss on drying, and related substances.

Stability data on 2 batches of the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions. Tests include those for appearance, pH, relative density and sterility.

J. Other Information

Shelf-life:
Shelf-life of the veterinary medicinal product as packaged for sale: 3 years
Shelf-life after first opening the immediate packaging: 28 days.

Special precautions for storage:
Do not freeze.
Keep the container in the outer carton in order to protect from light.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

Warnings and precautions as listed on the product literature are comparable to 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

The applicant provided bibliographical data, an overview of which appears in the sections below.

Pharmacodynamics

The major mechanism of action of barbiturates is depression of the central nervous system (CNS), with enhancement and mimicking of the action of the neurotransmitter gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the CNS. The action of barbiturates is to depress the cortex and probably thalamus of the brain in addition to the motor areas.

Oxygen consumption drops in the brain on application of barbiturates by up to 55%. Pentobarbital is a GABA-mimetic agent which binds the barbiturate receptor portion of the GABA receptor complex, with the rate of dissociation of GABA from its receptor decreasing in addition to the maintenance of chloride conductance. As the concentration of barbiturate increases, chloride channels are activated even without the presence of GABA. The GABA-dependent increase in chloride conductance may cause the hypnotic/sedative effects of barbiturates while GABA–independent increase induces anaesthesia.

Barbiturates usually decrease the transmission of nerve impulses at neuroeffector and synaptic junctions via the decrease in sensitivity of polysynaptic junctions due to the depolarising action of acetylcholine.

Pharmacokinetics

The pharmacokinetics of pentobarbital was studied after intravenous administration at 30 mg/kg, in five dogs. The elimination half-life was 8.2 ± 2.2 hours, steady-state volume of distribution was 1.08 ± 0.21 L/kg and elimination clearance was 0.0013 ± 0.004 L/min/kg. Threshold concentrations which suppressed the corneal response and instigated pain withdrawal were 26.4 ± 4.6 and 23.0 ± 2.9 ug/ml respectively. A further study investigated the metabolism of two forms of pentobarbital, *R*(+)- and *RS*-pentobarbital. Urine for dogs which had received *R*(+)-pentobarbital sodium showed two, similar, crystalline metabolites, yielded from the two forms.

Toxicological Studies

The applicant provided bibliographical data. The single dose toxicity of the active substance was considered the most important aspect of this potent and dangerous substance, which consequently must be treated with respect by the user.

- Single Dose Toxicity

  Acute toxicity and sleeping time studies were carried out in rats, using single doses of 100 mg/kg of five pentobarbital formulations. No drug-related adverse effects were noted post-mortem, confirming that euthanasia by pentobarbital would not interfere with pathological examinations in rats. In a further study, two species of rat were administered weekly with increasing doses (10 mg/kg per week) of pentobarbital, up to the dose lethal to all (LD100). There was no difference between the two groups with regard to the quantity of the lethal dose. A third study noted that injection directly into the liver of rats (0.05 ml/rat of a 50 mg/ml solution) caused haemorrhagic necrosis in animals euthanised 15, 30 or 45 minutes after injection. Focal necrosis and inflammatory cell infiltration was noted in animals euthanised at 30 and 45 minutes after injection. A significant increase in total bilirubin and the elevation of certain transaminases were also noted.

  Reports of the consumption of carcasses containing pentobarbital by dogs, (toxicosis) were given. In some cases the toxicosis was fatal. Pentobarbital is not rendered inactive by even a high increase in temperature.

- Repeated Dose Toxicity

  A table was provided which gave data on repeated dose toxicity studies in rats and mice. Changes were noted in the liver, in the rat at 441 mg/kg, and behavioural changes in the mouse were noted at 40 mg/kg.

- Reproductive Toxicity, including Teratogenicity

  Further references were provided which provided data on reproductive toxicity. One report cited that in golden hamsters, where doses ranged from 8, 16, 24 and 32 mg/100 g. Duration of anaesthesia ranged from 50, 140, 210 and 250 minutes respectively. At the highest dose of 32 mg/100 g, major changes were seen, with an increased resorption rate and a decreased foetal weight being observed. At 12 mg/ 100g, resorption was also noted.

  A further study looked at the administration of 40 mg or 80 mg/kg sodium pentobarbital in rats, given from day 9 to day 21 of pregnancy. In this negatively controlled study, some adverse effects were seen on dams receiving 80 mg/kg (decreased body weight), more male offspring were seen, and offspring had lowered brain-body ratios one year after the study.

  A final study observed the effects of sodium pentobarbital in hens, when given at 37 mg/kg, 14-15 hours prior to first second and fourth ovulations. A delay was noted in ovulation times.

- Mutagenicity

  A study in hamsters observed mated females which were anesthetised four to five hours before ovulation. Multiple factors determined any adverse events, including pentobarbital dose, degree of respiratory depression and route of administration.

- Carcinogenicity

  Pentobarbital was seen not to enhance any carcinogenic effects in studies in which liver carcinogenesis (established 6 weeks), had already been generated experimentally.

Observations in Humans

The applicant provided bibliographical data. In humans, pentobarbital has been used as a hypnotic and sedative, however barbiturates are not considered appropriate for such purposes. Barbiturates for pre-operative sedation have been replaced by other drugs. The data described suicide and attempted suicide by pentobarbital and T-61[2]. The characteristics of barbiturate poisoning in humans are: respiratory depression and coma, hypothermia and cardiovascular collapse. It has been found that an oral dose of 100 mg sodium pentobarbital induces a hypnotic effect. A perenteral solution for veterinary euthanasia may contain 300 mg/ml, thus the severe toxicity of even small doses of this product must be understood.

[2] T-61 – Euthanasia Solution containing pentobaribital (Canada).

User Safety

A user safety analysis provided the following information. To be found in the SPC:-

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.

Information for the health professional in case of exposure:
Emergency measures should be directed toward maintenance of respiration and cardiac function. In severe intoxication measures to enhance elimination of absorbed barbiturate may be necessary.

The concentration of pentobarbital in the product is such that the accidental injection or ingestion of quantities as small as 1ml in human adults can have serious CNS effects. A dose of pentobarbital sodium of 1g (equivalent to 2.5ml of product) has been reported to be fatal in humans. Treatment should be supportive with appropriate intensive therapy and maintaining the respiration.

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

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was required. The assessment concluded that for this well-known veterinary medicine, the environmental impact assessment stopped at Phase I step 3 for non-food animals, (cats, dogs, rodents, mink) and at Phase I step 5 for animals in a flock or a herd, (cattle horses ponies and pigs).

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

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted because animals receiving this product must never enter the food chain. The product is intended as a means of euthanasia to prevent suffering in the target species.

Withdrawal Periods

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 ASSESSMENT (EFFICACY)

Bioequivalence with the reference product was not demonstrated, but neither is the product ‘exempt’. It was agreed that due to the nature and intended use of the product and to avoid unnecessary use of experimental animals, the applicant’s justifications for omission of appropriate data is justified.

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

Published data were submitted, which emphasised the use of the intravenous route as the method of choice. Section 4.6 of the SPC reflects the pertinent

information for this product, which is intended for the purpose of euthanasia only:-

- Minor muscle twitching may occur after injection.
- Death may be delayed if the injection is administered perivascularly or into organs/tissues with low capacity for absorption. Barbiturates can be irritating when administered perivascularly.
- Pentobarbital sodium has the ability to cause induction excitement. Premedication/sedation significantly reduces the risk of experiencing induction excitement.
- Very occasionally one or a few gasping respirations occur after cardiac arrest. At this stage the animal is already clinically dead.

IV.B Clinical Studies

No studies were performed for this section of the application, due to the nature of the product. A series of references were submitted for analysis which related to the use of the correct dose for pentobarbital. The correct dosage is reflected 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 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)