College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
3531 AH Utrecht
The Netherlands

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Euthanimal 20%, 200 mg/ml, solution for injection

Euthanimal 40%, 400 mg/ml, solution for injection

Created: January 2020

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Alfasan Nederland B.V.	MRP
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MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0177/001-002/MR
Name, strength and pharmaceutical form	Euthanimal 20%, 200 mg/ml, solution for injection Euthanimal 40%, 400 mg/ml, solution for injection
Applicant	Alfasan Nederland BV Kuipersweg 9 3449 JA Woerden Nederland
Active substance(s)	Pentobarbital sodium
ATC Vetcode	QN51AA01
Target species	Pig, goat, sheep, cattle, horse, cat and dog
Indication for use	Euthanasia

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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).

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Full dossier application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	29 May 2013
Date product first authorised in the Reference Member State (MRP only)	Euthanimal 20%: 16 December 2003 Euthanimal 40%: 18 October 2012
Concerned Member States for original procedure	BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, HU, IE, IT, LT, LV, MT, PL, PT, RO, SE, SI, UK

I. SCIENTIFIC OVERVIEW

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.
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 of the product was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains 200 mg/ml or 400 mg/ml pentobarbital sodium and the following excipients: benzyl alcohol, ethanol 96%, propylene glycol, and water for injection. Cochineal red A is added as colourant.

The solution for injection is packed in 100 ml or 250 ml type II glass vials fitted with a bromobutyl stopper and secured with an aluminium cap.

The product represents 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 product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The product is manufactured according to a non-standard manufacturing process (aseptic filtration) using conventional manufacturing techniques.

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A process validation report has been included. The manufacturing process is completely validated.

The process validation data show that the formulation and manufacturing process of the product is fully under control to produce a product that meets the pre-set specifications and that no trends are present.

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.

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.

The excipients are in conformity with the requirements of their (Ph.Eur.) monographs.

The glass vials and stoppers are in conformity with the Ph.Eur. requirements.

D. Control on intermediate products

Not applicable.

E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The specification is 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.

F. Stability

The stability results from the Open Part of the ASMF confirm the retest period of the active substance when stored under the approved conditions.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout a shelf life of 3 years if stored below 25°C.

The claim of a 28 days stability after broaching if stored below at 2-8°C has been justified.

G. Other Information

None.

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III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that pentobarbital is a short-acting sedative and hypnotic. It causes depression of the central nervous system by GABA receptor modulation, imitating the action of Gamma-aminobutyric acid. Barbiturates suppress in particular the reticular activating system (RAS) in the brain, which normally ensures alertness. The immediate effect is the loss of consciousness followed by deep anaesthesia followed by, at high rates, rapid depression of the respiratory centre. Breathing stops and is quickly followed by cardiac arrest and rapid death.

The applicant has also provided bibliographical data which show that after intravenous administration fast distribution over the tissues will occur. Pentobarbital is mainly eliminated through the liver by biotransformation, particularly by the Cytochrome P450 system, as well as by excretion in the kidneys and redistribution. In pigs redistribution in fatty tissue might cause reduced plasma concentrations and prolonged action. Barbiturates may diffuse through the placenta in foetal tissue, and traces of barbiturates may be present in the breast milk.

Toxicological Studies

The applicant has provided bibliographical data. Only the single dose toxicity is relevant when the veterinary medicinal product is used according to the SPC.
Lethal dosages for pentobarbital when administered intravenously are: 80 mg/kg bodyweight in mice, 50 mg/kg bodyweight in rats, 45 mg/kg bodyweight in rabbits and 62 mg/kg bodyweight in dogs. The general recommended dose given for euthanasia in animals is given as 87 mg/kg.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that pentobarbital is very toxic and highly bioavailable after oral administration. Euthanimal 20%/40% may be irritating to the eyes and may cause hypersensitivity reactions. Embryotoxicity cannot be excluded.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

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Environmental Risk Assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines. The environmental risk assessment can stop in Phase I and no Phase II assessment is required because either the veterinary medicinal product will be used to treat a small number of animals in a flock or herd (individual animals), or when complete flocks or herds need to be euthanised, for example due to intervention after outbreak of zoonosis, all euthanised animals will be incinerated, preventing entry to the terrestrial environment.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical data to show that pentobarbital is a known active substance with a widely accepted indication of euthanasia in veterinary use. It belongs to the chemical group of barbiturates. Well known side effects are screaming, excitation and convulsions.

Tolerance in the Target Species of Animals

The bibliography provided shows that tolerance for pentobarbital exists by increased induction of the cytochrome P450 system in the liver.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

IV.B Clinical Studies

The applicant has provided results from five clinical studies. Two studies (in pigs and goats) were performed with Euthanimal 40%, and three studies (in pigs, cattle and horses) were performed with Dorminal 20% (registered in the Netherlands under marketing authorisation number REG NL 1965), which is proven bio-equivalent to Euthanimal 20%. When injected strictly intravenously Euthanimal 20%/40% will result in a fast collapse and in cardiac arrest within 2 min after administration. Details on the perfumed studies are presented in the table below.

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Study	**1**	**2**	**3**	**4**	**5**
Species	Cattle	Horses/ponies	Pigs	Goats	Pigs
Animals used	10 males	6 males, 6 females	5 males 5 females	20 females	21, (12 males, 6 females, 3 gender not recorded)
Treatment	Dorminal 20%, 50 mg pentobarbital/kg bodyweight	Dorminal 20%, 50 mg pentobarbital/kg bodyweight	Dorminal 20%, 100 mg pentobarbital/kg bodyweight	Euthanimal 40%, 100 mg pentobarbital/kg bodyweight	Euthanimal 40%, 100 mg pentobarbital/kg bodyweight
Administration route	Intravenous cathether	Intravenous cathether	Intracardial	Intravenous injection	Intravenous injection
Results (in seconds after administration)	Collapse: 18.3 s Apnoe/dyspnoe: 50.9 s Cardiac arrest: 84 s No cornea reflex: 86.6 s No signs of stress.	Collapse: 13.3 s Apnoe/dyspnoe: 19.1 s Cardiac arrest: 32 s No cornea reflex: 167.5 s No signs of stress.	Collapse: 9.6 s Apnoe/dyspnoe: 19.6 s Cardiac arrest: 83.3 s No cornea reflex: 31.7 s No pupil reflex: 31.6 s Urination and screaming recorded	Collapse: 11 s Apnoe/dyspnoe: 14 s Cardiac arrest: 69 s No cornea reflex: 66 s No pupil reflex: 37 s	Collapse: 8 s Apnoe/dyspnoe: 14 s Cardiac arrest: 80 s No cornea reflex: 29 s No pupil reflex: 16 s Screaming, convulsions, excitation recorded

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 risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

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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 Vetrinary Medicines 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.

Summary of change	**Section updated**	**Approval date**
Change in the pack size of the finished product within the range of the currently approved pack sizes: individual packages are added to the pack sizes (NL/V/0177/IA/001/G).	N/A	27 December 2013
Extension of the shelf life of the finished product as packaged for sale from 1 year to 3 years (NL/V/0177/IB/002/G).	Module 3, section II.F	24 July 2014
Renewal (NL/V/0177/001/R/001)	N/A	11 October 2017