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

RELEASE

Date: 2 October 2008

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0125/001/MR
Name, strength and pharmaceutical form	RELEASE, 300mg/ml, solution for injection,
Applicant	WDT Wirtschaftsgenossenschaft Deutscher Tierärzte Siemensstr. 14 30827 Garbsen Germany
Active substance(s)	Pentobarbital sodium
ATC Vetcode	QN51AA01
Target species	Horse, ponie, cattle, swine, dog, cat, mink, polecat, hare, rabbit, Guinea pig, hamster, rat, mice, chicken, pigeon, birds, snakes, tortoises, lizards, frogs,
Indication for use	For euthanasia in animals

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MODULE 2

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

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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 completion of the original Mutual recognition procedure	30.4.2008
Date product first authorised in the Reference Member State (MRP only)	23.4.2007
Concerned Member States for original procedure	Austria, Belgium, Hungary, Ireland, The Netherlands, United Kingdom

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 for the purpose of euthanasia in the target species; symptoms observed prior to death in animals are indicated in the SPC.

Food-producing animals euthanized with Pentobarbital must not be used for human consumption. 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 assessment of the product is in favour of granting a marketing authorisation.

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II. QUALITY ASPECTS

A. Composition

The product contains Pentobarbital Sodium (300(!) mg / ml) in a mixture of Ethanol, Propyleneglycole and Water for Injection

The product is filled into 50 and 100 ml uncoloured glass vials which allows for visual determination of particle contamination. The rubber stoppers are secured with aluminium crimp caps. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation is justified.

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 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.

An EDQM Certificate of Suitability (CoS) has been granted (R0-CEP 2002-061-Rev 01).

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 manufacture of this product.

E. Control on intermediate products

Section not relevant.

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

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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.

G. 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.

Stability data on 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.

The claim of a 63 days stability after broaching is based on the demonstration of stability for a batch broached and stored 63 days at 25°C.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

None.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

This is a hybrid type application according to Article 13 of Directive 2001/82/EC based on the essential similarity of the reference product Eutha 77, another pentobarbital sodium-containing injection solution for euthanasia in various animal species. The safety claims for Release 300 mg/ml are the same as those for the reference product. Therefore, results of toxicological tests are not required. However, additional precautionary measurements were included in the SPC of similar products containing pentobarbital-sodium to further minimize the risk for the user.

III.A Safety Testing

Pharmacological Studies

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See Part IV.A: Pre-Clinical Studies (Pharmacology)

Toxicological Studies

The applicant has provided bibliographical data which show the well-known pharmacodynamic and toxic effects of barbiturates. Pentobarbital causes death by severely depressing the medullary respiratory and vasomotor centres when administered at high doses. The lethal dose differs between target species. In general the twofold narcotic dose causes death. Fatal doses of pentobarbital cause some inflammation of the vital organs, congestion of the brain and meninges, and perivascular haemorrhage and oedema. For other toxicological endpoints like chronic toxicity, reproductive toxicity, mutagenicity and carcinogenicity no further data are required as Release 300 mg/ml with the active ingredient pentobarbital sodium is an agent for euthanasia and neither of the target species are foreseen for human or animal consumption.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the concentration of Pentobarbital sodium in the product is such that accidental self injection may have serious consequences to human health in particular serious CNS effects with potentially fatal outcome. Warnings and precautions as listed on the product literature are adequate to ensure safety of Release 300 mg/ml to the user.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that no special warnings are required.
Any unused veterinary medicinal product or waste materials is to be disposed of in accordance with local requirements.

III.B Residues documentation

Residue Studies
No residue depletion studies were conducted, because the product is only intended for euthanasia on the grounds of animal welfare. Food-producing animals euthanized with Pentobarbital must not be used for human consumption.

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MRLs

Pentobarbital, the active ingredient of the product, is not listed in Annex I, II or III of Council Regulation (EEC) 2377/90.

Withdrawal Periods

There is no withdrawal period for such a product. Adequate measures need to be taken to ensure that carcases of animals treated with pentobarbital and the by products of these animals do not enter the food chain and are not used for human consumption.

IV. CLINICAL ASSESSMENT (EFFICACY)

This is a hybrid type application according to Article 13(3) based on reference to another approved pentobarbital sodium-containing injection solution for euthanasia in various animal species. The efficacy claims for Release are equivalent to those of the reference product except for the target animals cattle and swine, which had not been authorised for the reference product when the marketing authorisation procedure for Release was ongoing. For these target animals bibliographic efficacy data have been provided.

IV.A Pre-Clinical Studies

Pharmacology
The applicant has provided bibliographical data to show that pentobarbital sodium like other barbiturates exerts its activity in all endothermic and ectothermic animal species in the central nervous system by a general depressant effect. The clinical consequences of injection of pentobarbital are dose dependant and consist in unconsciousness, respiratory and cardiac arrest and death due to hypoxia. For the purpose of euthanasia high doses of pentobarbital sodium are injected.

Pharmacokinetics
Pentobarbital-sodium reaches the central nervous system rapidly after injection and exerts its activity in a dose dependant manner.

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Tolerance in the Target Species of Animals

Target animal tolerance studies have not been submitted as the safe use of pentobarbital sodium is well established. Intravenous injection is the route of choice in all target animals under animal welfare aspects. Other injection routes may be associated with pain and death may enter with delay. Therefore, prior sedation is strictly recommended.

Bibliographical data have been provided regarding the new target species cattle and swine which show that pentobarbital when injected intravenously at the recommended doses produces death safely and with a minimum of distress. The product literature accurately reflects the type and incidence of side effects which might be expected.

IV.B Clinical Studies

The composition of Release is such that no negative impact on absorption is expected with respect to injection routes other than intravenous injection, when compared to the approved reference product. Moreover, doses well in excess to those producing unconsciousness in animals are recommended for euthanasia, thus guaranteeing a considerable margin of safety. Studies on bioavailability or on bioequivalence to the reference product have, therefore, not been requested.

Regarding the new target species cattle and pig the applicant has provided bibliographical data which show that, like in the other animal species, pentobarbital can be safety and effectively used for euthanasia in these target animals at the recommended doses as well.

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, euthanasia can be achieved in accordance with animal welfare requirements 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 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.

Quality changes

Summary of change (Application number)	**Section updated in Module 3**	**Approval date**
Change in fill volume (DE/V0125/001/II/005)	IIA	17/06/2017
Change of in-use stability (up to 63 days) (DE/V/0125/001/IB/008)	IIG	16/08/2019

Safety/efficacy changes

Summary of change (Type; application number)	**Section updated in Module 3**	**Approval date**
Harmonisation of the SPC and product literature after the repeat use procedure DE/V/0125/001/E/001. (DE/V/0125/001/II/002)	IIIA	02/06/2014
Implementation of changes to section 4.7 the SPC	N/A	24/09/2014

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requested by the RMS (DE/V/0125/001/IA/003)		

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