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Edificio 8
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Spain
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Caliermutin 2% premezcla (ES)

Caliermutin 20 mg/g premix for medicated feeding stuff for pigs and rabbits (PT)

MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0117/001/MR
Name, strength and pharmaceutical form	Caliermutin 2% premezcla (ES) Caliermutin 20 mg/g premix for medicated feeding stuff for pigs and rabbits (PT)
Applicant	Laboratorios Calier, S.A. C/Barcelonés, 26 (Plá del Ramassá) 08520 Les Franqueses del Vallés Barcelona-España
Active substance(s)	Tiamulin hydrogen fumarate
ATC Vetcode	QJ 01 XX 92
Target species	Porcine and rabbits
Indication for use	Porcine: Treatment and prevention of porcine dysentery caused by *B. hyodysenteriae*. Treatment of enzootic pneumonia caused by *M. hyopneumoniae*. Rabbits: Treatment and prevention of epizootic entercolitis.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v) website) (www.HEVRA.org).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual Recognition application in accordance with Article 12 of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	28th February 2007
Date product first authorised in the Reference Member State (MRP only)	6th February 2006
Concerned Member States for original procedure	Portugal

I. SCIENTIFIC OVERVIEW

For public assessment reports for the first authorisation in a range:

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, the consumer of foodstuffs from treated animals 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. Composition

The product contains as active substance Tiamulin hydrogen fumarate (20 mg) (Equivalent to 25 mg of Tiamulin hydrogen fumarate 80 %).
Excipients are: Sodium carboxymethylcellulose, Lactose, Soya-bean oil and Calcium carbonate.

The container/closure system is bags of 25 kg made of polyester-aluminium-nylon-polyethylene with a venting valve.

The particulars of the containers and controls performed are provided and conform to the regulation.

The pharmaceutical development is well documented. It justifies the chosen formulation and the manufacturing method to produce a homogeneous and stable premix, suitable for the proposed use.

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. A flow chart is enclosed in the dossier. The manufacturing equipment is detailed. The manufacturing process has been described.
Process validation data on the product have been presented in accordance with the relevant European guidelines in three pilot batches. Analysis certificates of three pilot batches and the three first commercial batches also support the suitability of the process to produce a homogeneous premix with a consistent quality.

C. Control of Starting Materials

The active substance is Tiamulin hydrogen fumarate, an established active substance described in the European Pharmacopoeia (01/2005:1659). 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 applicant justifies the quality of the raw material by means of an Active Substance Master File.

Soya-bean oil refined and calcium carbonate comply with the monographs number 01/2005:1473 and 04/2005:0014 of the European Pharmacopoeia, respectively. Certificates of analysis are submitted.

Lactose monohydrate and Sodium carboxymethylcellulose are described in Eur. Ph., and its quality has been documented in Part C.1.3. as part of the information submitted on Tiamulin Hydrogen Fumarate 80% coated.

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

Documentation from the suppliers to justify that starting materials have no risk of transmitting BSE are included.

E. Control on intermediate products

Not applicable.

F. Control Tests on the Finished Product

The routine controls have been considered enough for the proposed use of the finished product (medicated premix). In general, they have been designed according to procedures of the European pharmacopoeia. 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.

G. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines. Data obtained led to grant a shelf life of 3 years for both Tiamulin hydrogen fumarate and Tiamulin hydrogen fumarate 80% coated.

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 (12 months) without any specific condition of storage.

The Applicant did not include information on a shelf life period once opened the package. So, a warning of do not store the product in this condition was added to the SPC.

Stability studies according to the guideline EMEA/CVMP/080/95 “Additional quality requirements for products intended for incorporation into animal feedingstuffs” to justify a validity period of the product when incorporated to feed are presented up to 3 months.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics:

See Part IV

Pharmacokinetics:

The applicant has provided bibliographical data which show that tiamulin behaves as a lipophilic weak base. In addition, an evaluation of tiamulin concentrations in plasma, lung and intestinal content was performed by the company. In pigs, after oral administration, tiamulin is rapidly absorbed and the bioavailability is of 85%. It is widely distributed and extensively metabolised by several pathways (N-dealkylation, monohydroxylation, etc) in liver to metabolites that have poor antimicrobial activity. Elimination occurs via urine and faeces.

Considering rabbit as the minor specie, through the residues study carried out with rabbits and from the available data in other species, it is possible to assume that the metabolism in rabbit will not be significantly different and the extrapolation to other species is a valid assumption.

Toxicological Studies

The applicant has provided bibliographical data which show that tiamulin is of low toxicity when administered as a single oral dose to rats and medium toxicity for mice. Tiamulin was of high toxicity when administered intravenously.

Published information on the toxicity of tiamulin when administered to rats in feed for 26 weeks indicates that the main effects were on liver. The NOEL was 5 mg/kg bw/day. In dogs, after repeated oral administration for 26 weeks, the main effects were on liver and, in addition, electrocardiograms effects were observed. A NOEL of 3 mg/kg bw/day bases on this effect was established.

In rats, there were no overt signs of toxicity and no effects on behaviour or reproductive performance. There were no substance-related gross or histopathological changes in either the parent or the offspring. Several published information on the reproductive performance in pigs (breeding sows and breeding boars) indicated that there were no adverse effects. There was no evidence of teratogenic effect in laboratory animals following repeat oral administration.

Tiamulin did not induce gene mutations in Salmonella typhimurium strains TA 98, ta 100, TA 1535, TA 1537 and TA 1538. It also gave negative results in the in vitro assay for gene mutation at the HPRT locus of V79 Chinese hamster cells, and had no effect on the frequency of micronucleated polychromatic erythrocytes. Tiamulin was not genotoxic. There was no significant dose-related trend of the incidence of any tumour type.

Observations in Humans

Tiamulin is not used in human medicine.

Microbiological Studies

It is clearly pointed out that intestinal flora is highly exposed to Caliermutin given that it is administered via feed. Moreover, 90% of the dose is absorbed, and excretion route is primarily hepatic and via bile, therefore it achieves high concentrations in colon content. However, tiamulin is neither active against commensal organisms nor against alimentary pathogens. Consequently, its administration has no effect on the flora

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the higher risks of exposure to the product are inhalation or contact.

Concerning the inhalation route, tiamulin is irritant for the respiratory tract so appropriate preventive measures should be taken. A 0.05% formulation did not cause skin irritation or sensitisation, but precautions should be taken, anyway, like avoiding skin contact, using gloves when handling the product and washing the hands with water and soap after handling the molecule. Also protection glasses are to be used to avoid contact with the eyes. In case of contact, wash them with plenty of water.

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 further assessment was required. The applicant recalculated the PECsoil values taking into account that 83% of the medicinal product is widely metabolised (non active metabolites); moreover, the half-live of tiamulin in soil is stressed as reducing factor. The assessment concluded that there is no need to carry out studies on environmental effects as the recalculated PECsoil values (both piglets and fattening pigs) are < 100. Thus, together with some other evidences it seems to be assured that tiamulin will not tend to accumulate. No warnings regarding tiamulin are therefore required.

The SPC contains a standard phrase in section 6.6 as required.

III.B Residues documentation

Residue Studies

Residue depletion studies using the final formulation have been conducted in pigs and rabbits. Samples of tissues were taken from animals at several time points.

In pigs, results show that residues depleted to below the MRL in all tissues before the end of the withdrawal period. Statistical evaluation of the withdrawal period by the regression analysis was not possible. Therefore, the alternative method for the determination of withdrawal period has been used, by applying a safety margin of 40% to the last day when all residues were below MRL. A withdrawal period of 5 days has been obtained for Caliermutin 2% premix.

In rabbits, none of the sample tissues analysed showed tiamulin residues above the established MRL. A withdrawal period of 0 days has been obtained.

The analytical method was HPLC/LC-MS. The method was fully validated.

MRLs

Tiamulin is listed in Annex I of Council Regulation 2377/90 (Council Regulation 2728/1999 for porcine, and 2338/2000 for rabbits). The marker substance is the sum of metabolites that may be hydrolysed to 8-α-hydroxymutilin

MRLs are listed below:

	Porcine	Rabbit
Muscle	100 µg/kg	100 µg/kg
Liver	500 µg/kg	500 µg/kg

Withdrawal Periods

Based on the data provided above, a withdrawal period of 5 days for meat in pigs is justified. In rabbits, a withdrawal period of 0 days for meat is also justified.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies (pharmaceuticals only)

Pharmacology (if relevant – or delete)

Tiamulin is a diterpene antibiotic from the group of pleuromutilns. It is a bacteriostatic antibiotic which mode of action is based on the inhibition of protein synthesis in the target microorganisms. This action is due to the binding of the molecule to the bacterial ribosomal 50S subunit, close to the peptidyl transferase group. It has been described that tiamulin binds to this subunit in a 1:1 stoichiometry. The 50S subunit contributed predominantly to the binding energy that held the antibiotic to the ribosomes. The 30S subunit didn't show strong affinity for the drug but may be needed for the generation of the second binding site in the 70S particle. If depleted of ammonium ions, 70S ribosomes lost their binding capacity for the antibiotic. This mode of action has been widely described in the documentation provided by the applicant.

Antibacterial spectrum

The product, Caliermutin is intended for the prevention and treatment of porcine dysentery caused by *Brachyspira hyodysenteriae* and treatment of enzootic pneumonia caused by *Mycoplasma hyopneumoniae.*
The applicant provided different bibliographic documentation that support the susceptibility of the target micro-organisms mentioned above; In this documentation isolates from different European regions have been included. Besides the applicant carries out a study in Spain in order to show the in vitro sensitivity in the Mediterranean area. The study shows the different sensibility of tiamulin in different strains of target micro-organisms.

Tolerance in the Target Species of Animals

The applicant performed a study in order to assess the target specie tolerance. The objective was to evaluate the tolerance of the product administered in feed using multiples of the recommended dose in the target species.
During these days the general status of the animal (general health, behaviour, motor activity, appetite, digestive disorders and any adverse reactions) as well as feed and water consumption were controlled. Blood examples and blood chemistry were taken during the study.
All animals showed a good general health, normal behaviour; the weight gain of the pigs was around 100% in all groups. The analytical results were within normal values in all groups. The haematological and biochemistry results were very similar and very near to the registered previously in the bibliography. If compared the mean results between control animals and treated animals no significant differences between both groups were observed.

Besides the applicant provide several bibliographic data in relation to the general tolerance of the tiamulin and the same conclusions are arranged.

Resistance (if relevant – or delete)

The resistance of the causative agents (*Mycoplasma hyopneumoniae, Brachyspira hydysenteriae*) against tiamulin is supported by published papers.
The product, Caliermutin is intended for the prevention and treatment of porcine dysentery caused by *Brachyspira hyodysenteriae* and treatment of enzootic pneumonia caused by *Mycoplasma hyopneumoniae.*
The applicant provided different bibliographic documentation that support the susceptibility of the target micro-organisms mentioned above; In this documentation isolates from different European regions have been included. Besides the applicant carried out a study in Spain in order to show the in vitro sensitivity in the Mediterranean area. The study shows the different sensibility of tiamulin in different strains of target micro-organisms.

IV.B Clinical Studies (pharmaceuticals and immunologicals)

Field trials

The product is indicated for treatment and prevention of swine dysentery associated with B*rachyspira hyodysenteriae*, for treatment of epizootic enterocolitis in rabbit as well as for the treatment of mycoplasmal pneumonia caused by Mycoplasma hyopneumoniae. The applicant submitted several bibliographic references to support the product. Furthermore the applicant provides two field clinical trials to support the efficacy of the product by administering 8mg of tiamulin hydrogen fumarate per kg of body weight daily in the feed for 10 consecutive days for the treatment and 4 mg/kg body weight daily in the feed for 10 consecutive days. For rabbits the applicant presents three bibliographic studies to support the clinical efficacy of the product. All of these studies included the dose as ppm but taking into account the average intake of rabbits at the different ages, the dose rate recommended is 1.9 mg/Kg bw.
So based on bibliographic data and the two clinical trials provided by the applicant it can be concluded that tiamulin administered at the recommended dose and duration is effective against the above-mentioned causative agents.

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.