MINISTERIO DE SANIDAD Y CONSUMO
agencia española de medicamentos y productos sanitarios

SUBDIRECCIÓN GENERAL
DE MEDICAMENTOS
DE USO VETERINARIO

Agencia Española de Medicamentos y Productos Sanitarios

Parque Empresarial Las Mercedes
Edificio 8
C/Campezo 1,
28022 – Madrid
España
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

MACROMUTIN 125 mg/ml ORAL SOLUTION POULTRY AND PIGS

CORREO ELECTRÓNICO

mresvet@agemed.es

P. EMPRESARIAL LAS MERCEDES
C/ Campezo 1, Edificio 8
28022 MADRID
TEL: 91 822 54 01
FAX: 91 822 54 43

MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0123/001/MR
Name, strength and pharmaceutical form	Macromutin 125 mg/ml oral solution poultry and pigs
Applicant	LABORATORIOS CALIER, S.A. C/Barcelonés, 26 (Plá del Ramassá) 08520 Les Franqueses del Vallés Barcelona-España
Active substance(s)	Tiamulin hydrogen fumarate (THF)
ATC Vet code	QJ 01 XX 92
Target species	Poultry (Broilers, laying hens, breeder hens and turkeys) and Porcine.
Indication for use	<u>Poultry (Broilers, laying hens, breeder hens and turkeys):</u> Treatment and prevention of chronic respiratory disease (CRD) caused by tiamulin sensitive strains: *Mycoplasma gallisepticum*, *Mycoplasma meleagridis.* <u>Porcine:</u> Treatment of enzootic pneumonia caused by tiamulin sensitive strains: *Mycoplasma hyopneumoniae*, *Mycoplasma hyorhinis.* Treatment of haemorrhagic dysentery caused or complicated by tiamulin sensitive strains: *Brachyspira hyodysenteriae*

MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual Recognition application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	05/12/2007
Date product first authorised in the Reference Member State (MRP only)	12/04/2007
Concerned Member States for original procedure	PT

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 adverse 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 (101.2 mg)
(equivalent to125.0 mg of Tiamulin hydrogen fumarate)

Excipients are: methyl parahydroxybenzoate, propyl parahydroxybenzoate, citric acid monohydrate, ethanol (anhydrous), disodium phosphate dodecahydrate and purified water.

The container/closure system is high density polyethylene bottle, provided with K-50 stopper with strapping and welding disk.

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

The product is an aqueous solution to be administrated in drinking water. This pharmaceutical form complies with all the specifications of the European Pharmacopeia for oral solutions 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. A flow chart is enclosed in the dossier. The manufacturing equipment is detailed. The manufacturing process consists on a standardized blend of the components of the product.
Process validation data on the product have been presented in accordance with the relevant European guidelines. Analysis certificates of three pilot batches and the three first commercial batches also support the suitability of the process to produce a homogeneous oral solution for drinking water with a consistent quality.

C. Control of Starting Materials

The active substance is Tiamulin hydrogen fumarate 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 specifications are considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with these specifications have been provided.

The applicant justifies the quality of the raw material by means of an Active Substance Master File (ASMF Number TH/1462/05 in Spain, V-04/2006 in Portugal).

All the excipients Ethanol anhydrous (Ph. Eur. 2005:1318), citric acid monohydrate (Ph. Eur. 2005: 0456), disodium phosphate dodecahydrate (Ph. Eur. 2005:0118), metylparahydroxibenzoate (Ph. Eur. 2005: 0409), propyl parahydroxibenzoate (Ph.

Eur. 2005: 0431) and purified water (Ph. Eur 2005: 0008) comply with their corresponding monograph of European Pharmacopeia. Certificates of analysis are submitted.

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 (oral solution for drinking water). In general, they have been designed according to procedures of the European pharmacopoeia. The tests in the specifications, 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 have been provided demonstrating compliance with the specification.

G. Stability

Stability data on the active substance: Tiamulin hydrogen fumarate have been provided in accordance with applicable European guidelines, demonstrating the proposed re-test period of 3 years when stored in its original market container in dry and well-ventilated facilities protected from sunlight.

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 (18 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.

The stability of the product in drinking water have been documented according to the guideline EMEA/CVMP/540/03 Rev. The results of the study indicate that the parameters tested do not change during 24 hours, both in soft water or in hard water.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL) (*for pharmaceuticals only)*

This is a generic application according to Article 13(1) of Directive 2001/82/EC as amended, based on the essential similarity of Macromutin 125 mg/ml oral solution poultry and pigs and the approved precursor Tiamutin 12.5% w/v oral solution. The applicant is therefore exempted from presenting results of pharmacological and toxicological tests.

Normally, essential similarity has to be demonstrated by bioequivalence studies. In this case, no bioequivalence studies are necessary according the guideline for the conduct of bioequivalence studies for veterinary medicinal products (EMEA/CVMP/016/00-final), due to the same qualitative and quantitative composition and the same oral administration of Macromutin 125 mg/ml oral solution poultry and pigs and Tiamvet 12.5% w/v oral solution.

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that tiamulin hydrogen fumarate acts by inhibiting protein synthesis by reversibly binding to the 50 S ribosome subunit.

The applicant has also provided bibliographical data which show that tiamulin is rapidly absorbed after oral administration; the biovailability is, at least, 90%; it is distributed in lungs and colon; and 60-65% of tiamulin is excreted in the faeces with an entero-hepatic cycle, and 30-35% in the urine.

Toxicological Studies

As this is a generic application according to Article 13, results of toxicological tests are not required.

Other Studies

The applicant has provided bibliographical data and a comparative study between impurities of Macromutin 125 mg/ml oral solution poultry and pigs and impurities of the reference product, which show that the results are concordant.

Observations in Humans

Tiamulin hydrogen fumarate is not authorised for its use in human medicine.

Microbiological Studies (if relevant – or delete)

In case of tiamulin it is not considered to be necessary the study of microorganism included in the Guideline EMEA/CVMP/244/01-final, because tiamulin is not active against commensal organisms (*E. coli, Enterococcus faecium, Enterococcus faecails)* nor against food-borne pathogens (*Salmonella enterica* and *Campilobacter spp.)* so it has not impact on gut flora after its administration.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that tiamulin hydrogen fumarate is classified as irritant for the respiratory tract so the user should take appropriate preventive measures, as using an anti-dust mask. Topic administration of a 0.05% formulation did not cause skin irritation or sensitisation. However and due to the irritant character of the molecule precautions as avoid skin contact with the molecule using gloves when handling the product and wash hands with water and soap when finishing the work should be taken**.**

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 is required. The assessment concluded that the exposure levels to which the environmental organism of soil would be submitted is inferior to those maximum concentrations that would have an effect on those exposed species.
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 Macromutin 125 mg/ml oral solution poultry and pigs is a generic product, which reference product is Tiamutine solution 12.5% and it has been demonstrated that they are bioequivalent.

MRLs

Tiamulin is listed in Annex I of Council Regulation 2377/90.

MRLs are listed below:

Substance	Marker residue	Animal species	MRL (µg/kg)	Target tissues	Annex
Tiamulin	Sum of metabolites that may be hydrolysed to 8-α-hydroxymutilin	Porcine	100 500	Muscle Liver	I
		Poultry	100 100 1000 1000	Muscle Skin+fat Liver Eggs	I
		Turkeys	100 100 300	Muscle Skin+fat Liver	I

Withdrawal Periods

The withdrawal period is the same as stated in the reference product:

Pigs: 6 days
Broilers, laying hens and breeders: 6 days
Turkeys: 6 days
Eggs: 0 days

IV. CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13, 1) of Directive 2001/82/EC as amended, based on the bioequivalence of MACROMUTIN 12,5%ORAL SOLUTION and the reference product TIAMUTINE SOLUTION 12,5% efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

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.

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 veterinary Heads of Agencies website (www.HMA.eu).