AGENCE NATIONALE DU
MEDICAMENT VETERINAIRE

# PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

## KARIMULINA 125 mg/mL
## Solution for use in drinking water for rabbits

**DATE : 06/07/2023**

*French agency for food, environnemental and occupational health safety– French Agency for Veterinary Medicinal Products*
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# PRODUCT SUMMARY

| | |
|---|---|
| EU procedure number | FR/V/0456/001/DC |
| Name, strength and pharmaceutical form | KARIMULINA 125 mg/mL Solution for use in drinking water for rabbits |
| Applicant | KARIZOO<br>C/, MAS PUJADES, 11-12 POLIGONO INDUSTRIALE LA BORDA<br>08140 CALDES DE MONTBUI<br>SPAIN |
| Active substance(s) | Tiamulin |
| ATC vetcode | QJ01XQ01 |
| Target species | Rabbits |
| Indication for use | Reduction of mortality due to epizootic enteropathy in association with infections caused by *Clostridium perfringens*. |

| | |
|---|---|
| KARIMULINA | FR/V/0456/001/DC |
| LABORATORIOS KARIZOO | DCP |
| Publicly available assessment report | |

# PRODUCT INFORMATION

The Summary of Product Characteristics (SPC), the labelling and package leaflet for this veterinary medicinal product (VMP) is available in the Union Product Database (UPD).

# SUMMARY OF ASSESSMENT

| | |
|---|---|
| Legal basis of original application* | Generic application in accordance with Article 18 of Regulation (EU) 2019/6 as amended. |
| Reference product (RP) | CEVAMULINE SOLUTION LAPIN |
| Marketing authorisation holder | CEVA SANTE ANIMALE |
| Marketing authorisation number<br>EU procedure number | FR/V/9392718 9/2009<br>FR/V/0261/001/MR |
| Date of authorisation | 09/07/2009 |
| Date of completion of the original decentralised procedure | 03/05/2023 |
| Concerned Member States for original procedure | ES, IT, PT |

## 1. SCIENTIFIC OVERVIEW

The veterinary medicinal product (VMP) is produced and controlled using validated methods and tests, which ensure the consistency of the VMP released on the market.

It has been shown that the VMP can be safely used in the target species; the observed reactions are indicated in the SPC.

The VMP 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 VMP was demonstrated according to the claims made in the SPC.

The overall risk/benefit analysis is in favour of granting a marketing authorisation.

## 2. QUALITY DOCUMENTATION (physicochemical, biological or microbiological information)

### A. Product description

The VMP contains 101.2 mg/ml of tiamulin (as hydrogen fumarate) as active substance and the following excipients: propyl parahydroxybenzoate (E216), methyl parahydroxybenzoate (E218), citric acid monohydrate (E330), disodium phosphate dihydrate, ethanol 96% and purified water.

The container/closure system is as described on the SPC. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the adjuvants, the formulation and the presence of preservatives are justified.

The VMP is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

## B. Description of the manufacturing method

The VMP is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.

Process validation data on the VMP have been presented in accordance with the relevant European guidelines.

## C. Production and control of starting materials

The active substance is tiamulin hydrogen fumarate, an established substance described in the European Pharmacopeia. 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.

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this VMP.

## D. Control tests carried out on isolated intermediates during the manufacturing process

Not applicable.

## E. 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 VMP.

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 tests

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 VMP throughout its shelf life when stored under the approved conditions.

An in-use shelf-life and a shelf-life after dilution in drinking water as detailed on the SPC have been supported by appropriate data.

### G. Other information

Not applicable.

## 3. SAFETY DOCUMENTATION (safety and residues tests)

As this is a generic application according to Article 18 of Regulation (EC) 2019/6 and bioequivalence with a reference VMP has been demonstrated, results of safety tests are not required.

The toxicological/safety aspects of this VMP is/are identical to the reference VMP.

Warnings and precautions as listed on the product literature are the same as those of the reference VMP and are adequate to ensure safety of the product to users / the environment / consumers. Some specific warnings are included in regards of the risk to the environment.

### A. Safety tests

#### *Pharmacological studies*

As this is a generic application according to Article 18 of Regulation (EU) 2019/6, and bioequivalence with the reference product has been demonstrated, results of toxicological tests are not required.

#### *Toxicological studies*

As this is a generic application according to Article 18 of Regulation (EU) 2019/6, and bioequivalence with the reference product has been demonstrated, results of toxicological tests are not required.

#### *Development of resistance and related risk in humans*

The applicant has provided bibliographical information on the risk of resistance development and the potential spread of resistance in the environment resulting from the antimicrobial substance tiamulin. Warning regarding the persistence of tiamulin in soils appears on the product literature as this environmental property is an important factor for the potential spread of resistance.

### *User safety*

The applicant has provided a user safety assessment in compliance with the relevant guideline.

Warnings and precautions as listed on the product literature have been improved compared to those of the reference product.

### *Environmental Risk Assessment*

No environmental risk assessment has been performed. As the marketing authorization of the reference VMP was granted in France after 1st October 2005, this is acceptable.

## *B. Residues documentation*

### *Residue tests*

The applicant has not submitted residues data on the basis that bioequivalence with the reference product has been demonstrated.

### *Maximum Residue Limits*

The active substance tiamulin is an allowed substance as described in table 1 of the annex to Commission Regulation (EU) No 37/2010:

| TIAMULIN | | | | | | |
|---|---|---|---|---|---|---|
| Marker residue | Animal Species | MRL | Target Tissues | Other Provisions | Therapeutic Classification | Regulation |
| Sum of metabolites that may be hydrolysed to 8-α-hydroxymutilin | Porcine, **rabbit** | 100 µg/kg<br>500 µg/kg | Muscle<br>Liver | No entry | Anti-infectious agents/<br>Antibiotics | 37/2010 of 22.12.2009 |
| | Chicken | 100 µg/kg<br>100 µg/kg<br>1000 µg/kg | Muscle<br>Skin + fat<br>Liver | | | |
| | Turkey | 100 µg/kg<br>100 µg/kg<br>300 µg/kg | Muscle<br>Skin + fat<br>Liver | | | |
| tiamulin | Chicken | 1000 µg/kg | Eggs | | | |

An acceptable daily intake (ADI) was defined for tiamulin, of 30 µg/kg bw (*i.e.* 1800 µg/person).

### *Withdrawal Periods*

Based on the above provided data , a withdrawal period of 2 days for meat in rabbit is justified.

## 4. EFFICACY DOCUMENTATION (preclinical studies and clinical trials)

As this is a generic application according to Article 18 of Regulation (EC) 2019/6 and bioequivalence with a reference VMP has been demonstrated according section 7.1 of the European bioequivalence guideline, efficacy studies are not required. The efficacy claims for this VMP are equivalent to those of the reference VMP. The SPC has been updated in accordance with the Guideline on the summary of product characteristics (SPC) for veterinary medicinal products containing antimicrobial substances - EMA/CVMP/383441/2005-Rev.1.

### *A. Pre-Clinical Studies*

No pre-clinical studies were performed.

#### *Development of resistance and related risk in animals*

Bibliography on the development of resistance to tiamulin and on the level of resistance to pleuromutilins in rabbits was provided.

Adequate warnings and precautions appear on the product literature.

#### *Dose determination and confirmation*

No dose determination and confirmation studies are required since the bioequivalence of the candidate product to the reference product is considered demonstrated in accordance with the “Guideline on the conduct of bioequivalence studies for veterinary medicinal products” (EMA/CVMP/016/2000-Rev.4).

#### *Tolerance in the target species of animals*

This is an application for a generic product and the applicant has demonstrated bioequivalence with the reference product. No tolerance data were provided. It is accepted that the tolerance in the target species of the generic is comparable to that of the reference product. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

### *B. Clinical trials*

As this is a generic application according to Article 18 of Regulation (EC) 2019/6, clinical trials are not required to demonstrate the efficacy.

## 5. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the VMP 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 VMP for humans and the environment is acceptable.

## POST-AUTHORISATION PROCEDURES

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the VMP. The current SPC is available in the Union Product Database (UPD).

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 VMP.

None