SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

KARIDOX 100 mg/ml oral solution for use in drinking water for chickens and pigs [UK, ES, IT, NL, DK, RO]

DOXYSOL 10% [FR]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition per ml:

Doxycycline .....100 mg
(equivalent to Doxycycline hyclate 116.0 mg)

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Oral solution for use in drinking water.
Clear, dense, brownish-yellow solution.

4. CLINICAL PARTICULARS

4.1. Target species

Chicken (broilers) and pigs.

4.2. Indications for use, specifying the target species

CHICKENS (BROILERS)
Prevention and treatment of chronic respiratory disease (CRD) and mycoplasmosis caused by microorganisms sensitive to doxycycline.

PIGS
Prevention of clinical respiratory disease due to *Pasteurella multocida* and *Mycoplasma hyopneumoniae* sensitive to doxycycline.

The presence of the disease in the herd should be established before treatment.

4.3. Contraindications

Do not use in case of hypersensitivity to tetracyclines.
Do not use in case of resistance to tetracyclines occurs.
Do not use in animals with hepatic dysfunction.

4.4. Special warnings for each target species

Sick animals may have a reduced appetite and altered drinking patterns and should, if necessary, be medicated parenterally.
In cases of altered food or drinking water uptake, the concentrations should be adjusted in such a way that the recommended dosage is achieved.
Do not administer to laying hens.

4.5. Special precautions for use

Special precautions for use in animals

Prolonged or repeated use of this veterinary medicinal product is discouraged. Attention should be paid to avoidance of stressful conditions and improvement of management practices and hygiene standards.
Avoid administration in oxidised drinking equipment.
Use of the product should be based on susceptibility testing of the bacteria isolated from the animal. If this is not possible, therapy should be based on local (regional and farm level) epidemiological information about susceptibility of the target bacteria, taking into account official national antimicrobial policies.Inappropriate use of the product may increase the prevalence of bacteria resistant to doxycycline and may decrease the effectiveness of treatment with tetracyclines, due to the potential for cross-resistance.

Due to variability (time, geographical) in susceptibility of bacteria for doxycycline, bacteriological sampling and susceptibility testing of micro-organisms from diseased birds on farm are highly recommended.

A high resistance rate of *E.coli*, isolated from chickens, against tetracyclines has been documented. Therefore the product should be used for the treatment of infections caused by *E.coli* only after susceptibility testing has been carried out.

As eradication of the target pathogens may not be achieved, medication should therefore be combined with good management practices, e.g. good hygiene, proper ventilation, no overstocking.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

Tetracyclines may – in very rare cases – induce photosensitivity and allergic reactions.
Do not handle the product if you are hypersensitive to tetracyclines.
Wear gloves, work overall and approved safety glasses.
This product is acid and likely to be irritant. Avoid contact with skin and eyes. In case of contact with skin, rinse immediately with plenty of water. In case of contact with eyes, rinse immediately with copious amounts of water and seek medical advice.
Do not smoke, eat or drink while handling this product.
The product can be harmful by skin contact and inhalation and may cause eye irritation.
In case of accidental ingestion seek medical advise and show the label to the doctor.
If any symptom should appear, such as a cutaneous eruption, seek prompt medical advice. Swelling of the face, lips or eyes or respiratory difficulties are the most serious signs which require urgent medical attention.

4.6. Adverse reactions (frequency and seriousness)

Allergic and photosensitivity reactions can occur. Intestinal flora may be affected if treatment is very prolonged, and this may result in digestive disturbance.
If suspected adverse reactions occur, treatment should be discontinued.

4.7. Use during pregnancy, lactation or lay

The product should not be used during pregnancy or lactation

4.8. Interaction with other medicinal products and other forms of interaction

Doxycycline absorption may be reduced by the presence of high quantities of calcium, iron, magnesium or aluminium in the diet. Do not administer together with antacids, kaolin and iron preparations.
Do not administer together with bactericidal antibiotics.
The solubility of the product is pH dependent and will precipitate if mixed in alkaline solution
Do not administer with milk replacers

4.9. Amounts to be administered and administration route

To be administered in drinking water

- CHICKEN (broilers): 11.5 – 23 mg doxycycline hyclate / kg body weight / day, corresponding to 0.1 – 0.2 ml of the veterinary product per kg body weight, for 3-5 consecutive days
- PIGS: 11.5 mg doxycycline hyclate/ kg body weight / day, corresponding to 0.1 ml of the veterinary product per kg body weight,for 5 consecutive days).

Based on the recommended dose, and the number and weight of the animals to be treated, the exact daily amount of the veterinary product should be calculated according to the following formula:

$$\frac{\text{X ml veterinary product/ kg b.w./day} \times \text{Mean body weight (kg) of animals to be treated}}{\text{Mean daily water consumption (l) per animal}} = \text{X ml veterinary product per l drinking water}$$

To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing. The uptake of medicated water is dependant on the clinical condition of the animals. In order to obtain the correct dosage, the concentration in drinking water may have to be adjusted.

The use of suitably calibrated weighing equipment is recommended if part packs are used. The daily amount is to be added to the drinking water such that all medication will be consumed in 24 hours. Medicated drinking water should be freshly prepared every 24 hours. It is recommended to prepare a concentrated pre-solution – approximately 100 grams product per litre drinking water – and to dilute this further to therapeutic concentrations if required. Alternatively, the concentrated solution can be used in a proportional water medicator.
Medicated water should be the only drinking source.
The remaining medicated water should be disposed of in accordance with local requirements.

If no improvement in clinical signs is seen within the treatment duration, the diagnosis should be reviewed and treatment changed.

4.10. Overdose (symptoms, emergency procedures, antidotes)

No data available.

4.11. Withdrawal period

Meat & offal:
Chickens (broilers): 7 days
Pigs: 7 days.
Eggs: Not permitted for use in laying birds producing eggs for human consumption

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibiotic,Tetracyclines
ATCvet code: QJ01AA02

5.1. Pharmacodynamic properties

Doxycycline is a bacteriostatic agent that acts by interfering with the bacterial protein syntesis of sensitive species.
Doxycycline is a semi-synthetic tetracycline derived from oxytetracicline. It acts on the subunit 30S of the bacterial ribosome, to which is linked reversibly, blocking the union between aminoacyl-tRNA (transfer RNA) to the mRNA-ribosome complex, preventing the addition of new aminoacids into the growing peptide chain and thus interfering with protein synthesis.
Doxycycline is active against Gram-positive and Gram-negative bacteria.

Spectrum of activity:

Streptococcus spp.
Staphylococcus aureus
Chlamydia spp.
Mycoplasma spp.
Salmonella spp.
Pasteurella multocida

In vitro sensitivity of doxycycline against *Pasteurella multocida* and *Bordetella bronchiseptica* strains isolated from pigs has been determined by means of a plate diffusion method, and against *Mycoplasma hyopneumoniae* by a dilution method, with MIC_{90} values of 0.517 μg/ml, 0.053 μg/ml and 0.200 μg/ml, respectively.
According to the NCCLS standard, strains sensitive to doxycycline have MIC values below or equal to 4 μg/ml and those resistant have MIC values above or equal to 16 μg/ml.
There are at least two mechanisms of resistance to tetracyclines. The most important mechanism is due to decreased cellular accumulation of the drug. This is due to the establishment of either a pump elimination path or an alteration in the transport system that limits the uptake of tetracycline. The alteration in the transport system is produced by inducible proteins codified in plasmids and transposons. The other mechanism is evidenced by decreased ribosome affinitiy for the Tetracycline-Mg^{2+} complex owing to chromosomal mutations. Resistance to tetracyclines may not only be the result of therapy with tetracyclines, but may also be caused by therapy with other antibiotics leading to selection of multi-resistant strains including tetracyclines. Although minimal inhibitory concentrations (MIC) tend to be lower for doxycycline than for older generation tetracyclines, pathogens resistant to one tetracycline are generally also resistant to doxycycline (cross resistance). Both long term treatment and treating for an insufficient length of time and/or sub-therapeutic dosages can select for antimicrobial resistance and should be avoided.

5.2. Pharmacokinetic particulars

Doxycycline is bioavailable after oral administration. When orally administered, it reaches values greater than 70% in most species.
Feeding can modify the oral bioavailability of doxycycline. In fasting conditions bioavailability is around 10-15% greater than when the animal is fed.
Doxycycline is well distributed through the body as it is highly lipid soluble. It accumulated in liver, kidney, bones and intestine; enterohepatic recycling occurs. In lungs, it always reaches higher concentrations than in plasma. Therapeutic concentrations have been detected in aqueous humour, myocardium, reproductive tissues, brain and mammary gland. Plasma protein binding is 90-92%.
40% of the drug is metabolized and largely excreted through faeces (biliary and intestinal route), mainly as microbiologically inactive conjugates.

CHICKENS (broilers)
After oral administration, doxycycline is rapidly absorbed reaching maximum concentrations (C_{max}) around 1.5 h. Bioavailability was about 75%. The presence of food in the gastrointestinal tract reduces its absorption, reaching a bioavailability around 60% and extending considerably the time at which it reaches the maximum peak concentration, (t_{max}) 3.3 h.

PIGS
After an oral dose of 10 mg/kg/day, the concentration at steady state (Css) was around 1.30 µg/mL and plasma elimination half-life (t1/2) was 7.01 h.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Pyrrolidone
Propylene glycol

6.2. Incompatibilities

Do not mix with other veterinary medicinal products.

6.3. Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 15 months
Shelf life after dilution according to directions: 24 hours
Shelf-life after first opening the immediate packaging: 28 days

6.4. Special precautions for storage

Do not store above 25ºC.
Protect from light.

6.5. Nature and composition of immediate packaging

The product is packaged in white high-density polyethylene containers of 1 L and 5 L. Containers are closed with a screw cap of the same material with induction sealing.

6.6. Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Laboratorios Karizoo, S.A.
Polígono Industrial La Borda
Mas Pujades, 11-12
08140 – Caldes de Montbui (Barcelona)
SPAIN

8. MARKETING AUTHORISATION NUMBER

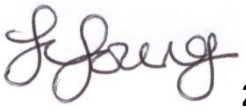
Vm 31223/4000

9. DATE OF FIRST AUTHORISATION

20 August 2008

10. DATE OF REVISION OF THE TEXT

May 2013

Approved:  **23/05/2013**