SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Karidox 500 mg/g powder for use in drinking water for pigs, chickens and turkeys [ES, NL, HU, PL, PT, RO, LT]
Karidox Doxycycline 500 mg/g Powder for use in Drinking Water for Pigs, Chickens and Turkeys [UK]
Beladox 500 mg/g powder for use in drinking water for pigs, chickens and turkeys [DE]
Supradox 500 mg/g powder for use in drinking water for pigs, chickens and turkeys [DK]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram contains:

Active substance:
Doxycycline 500.0 mg
(equivalent to Doxycycline hyclate 580.0 mg)

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for use in drinking water
Yellowish powder.

4. CLINICAL PARTICULARS

4.1 Target species

Pigs (fattening pigs after weaning), chickens (broilers, broiler breeders) and turkeys (broilers, breeders).

4.2 Indications for use, specifying the target species

Pigs (fattening pigs after weaning): treatment of clinical respiratory infections caused by *Mycoplasma hyopneumoniae* and *Pasteurella multocida* susceptible to doxycycline.
Chickens (broilers, broiler breeders) and turkeys (broilers, breeders): treatment of clinical respiratory infections associated with *Mycoplasma gallisepticum* susceptible to doxycycline.

4.3 Contraindications

Do not use in case of hypersensitivity to the active substance or to any of the excipients.
Do not use in animals with hepatic dysfunction.

4.4 Special warnings for each target species

The uptake of medication by animals can be altered as a consequence of illness. In case of insufficient uptake of drinking water, animals should be treated parenterally.

4.5 Special precautions for use

i. Special precautions for use in animals

Inappropriate use of the product may increase the prevalence of bacteria resistant to tetracycline due to the potential for cross resistance.
Use of the product should be based on susceptibility testing and take into account official and local antimicrobial policies.
The safety of the product has not been established in piglets before weaning.
Avoid administration in oxidized drinking equipment.
Do not use when tetracycline resistance has been detected in the herd/flock 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.

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

During preparation and administration direct contact of the product with the skin, eyes and mucous membranes and inhalation of dust particles should be avoided.
People with known hypersensitivity to tetracyclines should avoid contact with the veterinary medicinal product.
Wear protective gloves (e.g. rubber or latex), goggles and an approppriate dust mask (either a disposable half-mask respirator conforming to European Standard EN 149 or a non-disposable respirator to European Standard EN 140 with a filter to EN 143), when reconstituting or administering the solution. Wash exposed skin after preparation. In case of accidental

projection into the eyes, rinse abundantly with water. Do not smoke, eat or drink when handling the product.
In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician. Inflammation 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)

As for all tetracyclines, on rare occasions allergic reactions and photosensitivity may occur. If suspected adverse reactions occur, treatment should be discontinued.

4.7 Use during pregnancy, lactation or lay

Laboratory studies in rats and rabbits have not produced any evidence of a teratogenic, foetotoxic, maternotoxic effects.
The safety of the product has not been established in pregnant or lactating sows. The use is not recommended during pregnancy and lactation.
Do not use in birds in lay and within 4 weeks before the onset of the laying period.

4.8 Interaction with other medicinal products and other forms of interaction

Do not administer concurrently with feed overloaded with polyvalent cations such as Ca^{2+}, Mg^{2+}, Zn^{2+} and Fe^{3+} because the formation of doxycycline complexes with these cations is possible. Do not administer together with antacids, kaolin and iron preparations as tetracyclines are bacteriostatic antimicrobials, do not administer in conjunction with bactericidal antibiotics like beta-lactames. It is advised that the interval between administration of other products containing polyvalent cations should be 1-2 hours because they limit the absorption of tetracycline.
Doxycycline increases the action of anticoagulants.

4.9 Amounts to be administered and administration route

To be administered in drinking water.
In pigs and chickens, 23.1 mg doxycycline hyclate per kg of body weight daily (equivalent to 40.0 mg product per kg of body weight), administered in the drinking water for 5 consecutive days.
In turkeys, 28.8 mg doxycycline hyclate per kg of body weight daily (equivalent to 50.0 mg product per kg of body weight), administered in the drinking water 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:

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

animal

To ensure a correct dosage body weight should be determined as accurately as possible. 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. It is recommended to prepare a concentrated pre-solution 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 refreshed every 24 hours. The medicated water should be the only source of drinking water, throughout the treatment period. The medicated water must not be prepared or stored in a metal container.
The maximum solubility of the product in water is 72 g/L. Solubility of the product is pH dependent and it will precipitate if it is mixed in an alkaline solution.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

During the target animal tolerance study, no adverse effect was observed even at the fivefold therapeutic dose administered for two times the recommended duration in either target animal species.
If suspected toxic reactions do occur due to extreme overdose, the medication should be discontinued and appropriate symptomatic treatment should be initiated if necessary.

4.11 Withdrawal period(s)

Pigs:	Meat and offal:	4 days
Chickens:	Meat and offal:	5 days
Turkeys:	Meat and offal:	12 days

Not permitted for use in laying birds producing eggs for human consumption.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antiinfectives for systemic use, tetracyclines.
ATCvet code: QJ01AA02

5.1 Pharmacodynamic properties

Doxycycline is a semisynthetic tetracycline derivative. It acts by inhibiting protein synthesis at the ribosomal level, predominantly by binding to the 30S ribosomal subunits of bacteria. Doxycycline is a broad-spectrum antibiotic. It exhibits a wide range of activity against gram-positive and gram-negative, aerobic and anaerobic pathogens, especially against *Pasteurella multocida* and *Mycoplasma hyopneumoniae* isolated from pig respiratory infections and *Mycoplasma gallisepticum* associated with clinical respiratory infections in

chickens and turkeys. The MIC_{90} values of doxycycline against *Mycoplasma hyopneumoniae* strains isolated in Spain (2001) and in Belgium (2000-2002) were determined as 0.2 and 0.5 µg/ml, respectively. The MIC_{90} values for *Pasteurella multocida* isolated in France and the United Kingdom (2002-2004), and Germany (2004-2006) were found to be 2.0 µg/mL. The MIC_{90} of doxycycline against *M. gallisepticum* strains isolated in France, Germany and Hungary (2003-2009) was reported 0.5 µg/ml.
Resistance is mostly due to interference with the active transport of the tetracyclines into, and increased efflux from the cells, or ribosomal protection in which protein synthesis becomes resistant to inhibition. Basically there is a complete cross-resistance within the class of tetracyclines. Doxycycline may be effective against certain strains resistant to conventional tetracyclines due to ribosomal protection or efflux pump mechanisms.
According to the CLSI regulation, organisms other than streptococci with MIC values ≤ 4µg/ml are considered sensitive, at 8 µg/ml intermediate and with MIC values ≥16µg/m resistant to doxycycline.

5.2 Pharmacokinetic particulars

After oral administration to **pigs**, doxycycline is substantially absorbed from the gastrointestinal tract. The binding rate to plasma proteins is 93%. It is widely distributed in the organisms; at the steady state, the volume of distribution (VSS) is 1.2 L/kg. Doxycycline is not metabolised to any significant extent and it is excreted primarily in faeces, mostly in a microbiologically inactive form. The elimination half-life was reported to be 4-4.2 hours. The steady-state plasma concentrations ranged from 1.0 and 1.5 µg/ml. Both the lung and nasal mucosa concentrations at steady-state were higher than the plasma level. The ratio between tissue and plasma concentration was found to be 1.3 for lung and 3.4 for nasal mucosa. The doxycycline concentrations both in the lung and the nasal mucosa exceeded the MIC_{90} of the drug against the target respiratory pathogens.
Pharmacokinetics of doxycycline after single oral administration to **chickens** is characterised by a quite rapid and substantial absorption from the gastrointestinal tract providing peak plasma concentrations between 0.4 and 3.3 hours depending on age and the presence of food. The drug is widely distributed in the organism with Vd values close to or greater than 1, and exhibits an elimination half-life of 4.8 to 9.4 hours. The protein binding ratio at therapeutic plasma concentrations is in the range of 70-85%. The bioavailability in chickens may vary between 41 and 73%, also depending on the age and feeding. The presence of food in the gastrointestinal tract determines a lower bioavailability compared to that obtained in the fasted state.
The average plasma concentrations over the whole treatment period were reported 1.86±0.71 µg/m.
Pharmacokinetics of doxycycline after single oral administration to **turkeys** is characterised by a quite rapid and substantial absorption from the gastrointestinal tract providing peak plasma concentrations between 1.5 and 7.5 hours depending on age and the presence of food. The drug is widely distributed in the organism with Vd values close to or greater than 1, and exhibits an elimination half-life of 7.9 to 10.8 hours. The protein binding ratio at therapeutic plasma concentrations is in the range of 70-85%. The bioavailability may vary between 25 and 64%, also depending on the age and feeding. The

presence of food in the gastrointestinal tract determines a lower bioavailability compared to that obtained in the fasted state.
The average plasma concentrations over the whole treatment period were reported 2.24±1.02 µg/ml.
In both avian species the PK/PD analysis of fAUC/MIC_{90} data resulted in >24 h values that meet the requirements for tetracyclines.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid anhydrous.
Lactose monohydrate.

6.2 Incompatibilities

Doxycycline may form insoluble complexes with divalent ions, especially iron or calcium, zinc and magnesium.

6.3 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 18 months
Shelf-life after first opening the immediate packaging: 3 months
Shelf-life after dilution or reconstitution according to directions: 24 hours

6.4. Special precautions for storage

Do not store above 25ºC.

6.5 Nature and composition of immediate packaging

The veterinary medicinal product is packaged in thermosealed bags of 200 g and 1 kg. Bags are made of polyester, aluminium and polyethylene complex.
Not all pack sizes may be marketed.

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 31223/4001

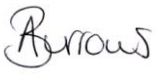
9. DATE OF FIRST AUTHORISATION

21 December 2012

10. DATE OF REVISION OF THE TEXT

December 2012

PROHIBITION OF SALE, SUPPLY AND/OR USE
To be supplied only on veterinary prescription

Approved:  **21/12/2012**