SUMMARY OF PRODUCTS CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

DOXYCYCLINE CALIER 500 mg/g powder for use in drinking water for chickens, turkeys and pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram contains:
Active substance:
Doxycycline (as doxycycline hyclate) *500 mg*

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for use in drinking water.
Yellow powder.

4. CLINICAL PARTICULARS

4.1 Target species:

Chickens (broilers)
Pigs (fattening pigs)
Turkeys

4.2 Indications for use, specifying the target species

Chickens (broilers) and turkeys: Prevention and treatment of Chronic Respiratory Disease (CRD) caused by *Mycoplasma gallisepticum* susceptible to doxycyclin*.*

Pigs (fattening pigs): prevention and treatment of clinical respiratory infection caused by sensitive strains of *Pasteurella multocida* susceptible to doxycyclin.

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, farm level) epidemiological information about susceptibility of the target bacteria.

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

4.3 Contraindications:

Do not use in case of hypersensitivity to the active substance or to any excipient.
Do not use in animals with hepatic disorders
Do not use in animals with renal disorders
See section 4.7.

4.4 Special warnings for each target specie

Under-dosing and/or treating for an insufficient length of time are considered to promote the development of resistance in bacteria and should be avoided.
Sick animals may have a reduced appetite and an altered drinking pattern and should, if necessary, be medicated parenterally.

4.5 Special precautions for use:

Special precautions for use in animals
Avoid administration in oxidised drinking equipment.

Due to likely variability (time, geographical) in susceptibility of bacteria to doxycycline, bacteriological sampling and susceptibility testing are recommended.

Inappropriate use of the veterinary medicinal product may increase the prevalence of bacteria resistant to doxycycline and may decrease the effectiveness of treatment with other tetracyclines due to the potential for cross-resistance.

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.

Do not use at concentrations lower than 0.23 g of powder /l in drinking water with pH higher or equal to 7.5 to avoid precipitation.

Do not add acid to the medicated drinking water.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
If you know you are allergic to the tetracycline class of antibiotics, special care should be taken when handling this product or the medicated solution.

During preparation and administration of the medicated drinking water, skin contact with the product and inhalation of dust particles should be avoided. Wear impermeable gloves (e.g. rubber or latex) and an appropriate dust mask (e.g. disposable half-mask respirator conforming to European Standard EN149) when applying the product.

In the event of eye or skin contact, rinse the affected area with large amounts of clean water and if irritation occurs, seek medical attention. Wash hands and contaminated skin immediately after handling the product.

If you develop symptoms following exposure such as skin rash, you should seek medical advice and show this warning to the physician. Swelling of the face, lips or eyes, or difficulty with breathing are more serious symptoms and require urgent medical attention.

Do not smoke, eat or drink while handling the product.
Take measures to avoid producing dust when incorporating the product into water. Avoid direct contact with skin and eyes when handling the product to prevent sensitisation and contact dermatitis.

4.6 Adverse reactions (frequency and seriousness):

In the case of allergic and/or photosensitivity reactions, the withdrawal of the treatment should be recommended.
Intestinal flora may be affected if treatment is very prolonged, and this may result in digestive disorder.
If suspected adverse reactions occur, treatment should be discontinued. Inform your veterinary surgeon if adverse reactions occur that are not indicated**.**

4.7 Use during pregnancy and lactation or lay:
Laboratory studies in rats and rabbits have not produced any evidence of a teratogenic, foetotoxic, maternotoxic effects of doxycycline.
However, the safety of the veterinary medicinal product has not been established in pregnant or lactating sows.
The veterinary medicinal product should not be used during pregnancy or lactation

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.

Chickens (broilers): 20 mg doxycycline / kg b.w. / day (corresponding to 40 mg ofproduct / kg b.w. / day), for 3-5 days

Turkeys: 20 mg doxycycline / kg b.w. / day (corresponding to 40 mg ofproduct / kg b.w. / day), for 5 days.

Pig (fattening pigs): 10 mg doxycycline / kg b.w. / day (corresponding to 20 mg of product / kg b.w. / day), for 5 days

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

$$\frac{\text{…… mg product/ kg bodyweight / day} \times \text{Mean body weight (kg) of the animals to be treated}}{\text{Mean daily water consumption (l) per animal}} = \text{…..mg of product per l drinking water}$$

To ensure a correct dosage body weight should be determined as accurately as possible.

The uptake of medicated water is dependant on the clinical conditions of the animals. In order to obtain the correct dosage, the concentration in drinking water may have to be adjusted.

Do not use at concentrations lower than 0.23 g of powder /l in drinking water with pH higher or equal to 7.5 to avoid precipitation.

Sufficient access to the system of water supply should be available for the animals to be treated to ensure adequate water consumption. No other source of drinking water should be available during the medication period.
Only sufficient medicated drinking water should be prepared to cover daily requirements.

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.

4.10 Overdosage (symptoms, emergency procedures, antidotes)

The administration of 40 mg/kg bw in pigs and 80 mg/kg in chickens (in both species 4 times the recommended dose), for 5 days did no cause any adverse reaction.

In case of overdose treatment should be suspended and symptomatic treatment established.

4.11 Withdrawal period

Pigs:
Meat and offal: 6 days

Chickens:
Meat and offal: 6 days
Eggs: Not authorized for use in laying birds producing eggs for human consumption.

Turkeys
Meat and offal: 9 days
Eggs: Not authorized for use in laying birds producing eggs for human consumption.

5. PHARMACOLOGICAL PROPERTIES

ATCvet code: QJ01AA02. Doxycycline.
Pharmacotherapeutic group: Antibacterials for systemic use; tetracyclines

5.1 Pharmacodynamic properties:

Doxycycline is a bacteriostatic antibiotic that acts by interfering with the bacterial protein synthesis of sensitive species.

Doxycycline is a semi-synthetic tetracycline derived from oxytetracycline. It acts on the subunit 30 S of the bacterial ribosome, to which is bound 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 an thus interfering with protein synthesis.

Doxycycline is active against *Mycoplasma spp*. (chickens and turkeys), and *Pasteurella multocida* (fattening pigs).

Sensitivity of Doxycycline against *Pasteurella multocida* strains isolated from fattening pigs in 2004 has been determined, by means of agar dilution method. MIC_{90} values found are shown in next table (source of breakpoints: NCCLS 2000).
Concentration range used: 0.065 – 16 μg/ml.

NCCLS 2000	*Pasteurella multocida*
MIC_{90}	0.250
Breakpoints	Sensitive ≤ 4μg/ml

MIC_{90} of microorganisms involved in porcine respiratory complex

Sensitivity of Doxycycline against *Mycoplasma gallisepticum* strains isolated from turkeys between 2007 - 2010 has been determined, by means of agar dilution method. MIC_{90} values found are shown in next table.

Strains	**MIC_{90} Ug/ml**
M.gallisepticum	0.5

There are at least two mechanism of resistance to tetracyclines:

One mechanism is evidenced by decreased ribosome affinity for the tetracycline-Mg^{2+} complex owing to chromosomal mutations. It is a ribosomal protection mechanism, in which protein synthesis is resistant to inhibition through a cytoplasmic protein (Prescott et al., 2000).
The most important mechanism of acquired resistance to tetracyclines is plasmid mediated, and is evidenced by a decrease in the cellular accumulation of the drug. The basis of this decrease is a reduction of the active transport of tetracyclines into the cell due to alterations of the external cellular membrane and increased efflux (or active pump elimination) by acquisition of new transport systems of cytoplasmic membrane. (Prescott et al., 2000). The alteration in the transport system is produced by inducible proteins codified in plasmids and transposons. Because the action mechanism of all tetracyclines has the same base, when resistance occurs, normally there is cross-resistance and complete within its group.

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 reaches well irrigated tissues as well as peripheral ones. It accumulates 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 drug is metabolized and largely excreted through faeces (biliary and intestinal route), mainly as microbiologically inactive conjugates.

CHICKENS

After oral administration, doxycycline is quickly absorbed; achieving maximum concentrations (Cmax) around 1.5 h. Bioavailability is 75%. Absorption is decreased in the presence of aliment in gastrointestinal tract, bioavailability is then around 60% and the time to achieve the maximum concentration peak is significantly elongated, (Tmax) 3.3 h.

FATTENING PIGS

Treatment with the recommended dosage, maximum blood concentration in steady state ($C_{max\text{-}ss}$) was 0.83 μg/ml (SD = 0.29), minimum blood concentration in steady state ($C_{min–ss}$) was 0.22 and $C_{ave\text{-}ss}$= 0.49

After oral administration of 10 mg doxycycline /kg bw in pigs the bioavailability was 24.8 ± 4.6%. The elimination half-life ($t_{1/2}$) was 4.6 h; plasmatic clearance was 0.15 l/h.kg and apparent distribution volume was 0.89 l/kg.

TURKEYS

Treatment with the recommended dosage, maximum blood concentration in steady state ($C_{max\text{-}ss}$) was 4.12 μg/ml (, minimum blood concentration in steady state ($C_{ave\text{-}ss}$) was 2.27 μg/ml and AUC_{ss}= 241.5 μg.h/ml.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Citric acid anhydrous

6.2 . Incompatibilities

In absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products

6.3 Shelf-life:
Shelf-life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after dilution in drinking water: 24 hours.
After first opening the immediate packaging, discard the unused veterinary medicinal product.

6.4 Special precautions for storage:
This veterinary medicinal product does not require any special storage conditions.

6.5 Nature and composition of immediate packaging:
Heat-sealed bag of 1 kg formed from polyester/aluminium/low density polyethylene laminate
Cardboard drums containing 5 bags of 1 kg.
Box containing 10 bags of 1 Kg
Cardboard drums containing 25 bags of 1 kg.

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 CALIER, S.A.
C/. Barcelonés, 26 (Pla del Ramassà)
LES FRANQUESES DEL VALLES, (Barcelona).

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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