

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Doxycycline Calier 125 mg/g Premix for medicated feeding stuff for pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each g contains:

Active substance:

Doxycycline (hyclate) 125 mg

Excipients:

Shelled almond flour 167 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Premix for medicated feeding stuff

Yellowish-white granulated powder

4. CLINICAL PARTICULARS

4.1 Target species

Pig (pig for fattening)

4.2 Indications for use, specifying the target species

Treatment and metaphylaxis of clinical respiratory infections caused by *Actinobacillus pleuropneumoniae* strains susceptible to doxycycline.

The presence of the disease in the group/flock must be established before the product is used.

4.3 Contraindications

Do not use in cases of hypersensitivity to the active substance or to any excipient.

Do not use in animals with hepatic dysfunction.

Please see section 4.7.

4.4 Special warnings for each target species

Feed intake is dependent on the clinical conditions of the animal. In case of insufficient feed ingestion, animals should be treated by parenteral route.

4.5 Special precautions for use

Special precautions for use in animals

Use of the veterinary medicinal product should be based on susceptibility testing and take into account official and local antimicrobial policies.

Use of the product deviating from the instructions given in the SPC 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.

In order to avoid stress conditions, best handling measures should be taking into account, specially hygiene, ventilation and animals handling.

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

People with known hypersensitivity to tetracyclines should avoid contact with the veterinary medicinal product.

Handle this veterinary medicinal product with care to avoid inhalation of dust particles and skin and eye contact during the incorporation of the premix into feed, taking into account the following specific recommendations:

- Take adequate measures to avoid dust formation when incorporating the veterinary medicinal product into feed.
- Personal protective equipment consisting of a dust mask (in accordance with EN140FFP1), gloves, overalls and approved safety goggles should be worn when handling the veterinary medicinal product.
- Direct contact of the veterinary medicinal product with the skin, eyes and mucous membranes should be avoided. In case of accidental exposure rinse abundantly with water.
- Do not smoke, eat or drink when handling the veterinary medicinal product.

In case of accidental ingestion or if you develop symptoms following exposure such as skin rash, you should seek medical advice 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, allergic reactions and photosensitivity are uncommon. Intestinal flora may be affected in uncommon occasions if treatment is very prolonged, and this may result in digestive disorder in uncommon occasions.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated report)

4.7 Use during pregnancy, lactation or lay

Pregnancy: Laboratory studies in laboratory animals (rats and rabbits) have not demonstrated toxic effects. The safety of the product has not been established in pregnant sows. The use is not recommended during pregnancy. Do not use in breeding animals

Lactation: The safety of the product has not been established in lactating sows. The use is not recommended during lactation. Do not use in breeding animals.

Fertility: Do not use in breeding animals.

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+} , Al and Fe^{2+} because the formation of doxycycline complexes with these cations is possible. Do not administer together with kaolin and iron preparations.

4.9 Amounts to be administered and administration route

In feed use.

Dosage:

10 - 12 mg doxycycline per kg of body weight daily, equivalent to 80 – 95 mg veterinary medicinal product /kg bw/day, for 8 days.

Administration:

Due to the intake of feed will vary depending on the clinical condition of the animals and the administration form, in order to obtain the correct dosage the concentration of doxycycline has to be adjusted accordingly. To calculate the dosage of the veterinary medicinal product, the following formula could be used as an example:

$$\frac{80 - 95 \text{ mg veterinary medicinal product per kg bw/ day} \times \text{Average pig body weight (kg)}}{\text{Average daily feed intake (kg/animal)}} = \text{mg veterinary medicinal product / per kg of feed}$$

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

The recommended incorporation rate in feed would be 2 kg of veterinary medicinal product per Tn of feed.

Pelletisation of medicated feed has to be carried out at a temperature not exceeding 80° C.

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

Not described.

4.11 Withdrawal period(s)

Pigs (fattening pigs):

Meat: 5 days

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use. Tetracyclines.

ATCvet code: QJ01AA02

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 and thus interfering with protein synthesis. Doxycycline has a bacteriostatic activity.

Doxycycline is active against gram-positive and gram-negative pathogens, especially against *Actinobacillus pleuropneumoniae*.

There are at least two mechanism of resistance to tetracyclines. The most important mechanism 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. The alteration in the transport system is produced by inducible proteins codified in plasmids and transposons.

The other mechanism is evidenced by decreased ribosome affinity for the tetracycline-Mg²⁺ complex owing to chromosomal mutations.

Because the action mechanism of all tetracyclines has the same base, when resistance occurs, normally there is cross-resistance and complete within its group.

<i>Critical concentrations (breakpoints) of sensitive (S) or resistance (R) in µg/ml of tetracycline: (Source: CLSI 2008)</i>	S		R
<i>Bacteria different from streptococci</i>	≤ 4	8	≥ 16

5.2 Pharmacokinetic particulars

Absorption, after oral administration is high (67%). 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.

40% of drug is metabolized and largely excreted through faeces (biliary and intestinal route), mainly as microbiologically inactive conjugates.

FATTENING PIGS

After oral administration to pigs at a single dose of 10 mg/kg bw, the peak serum concentration was of 1.5 µg/ml reached between 6 and 8 hours after dosing. The elimination plasmatic half-life was reported to be 23.54 hours.

After feed oral administration of 250 mg doxycycline /kg bw in pigs, administered ad libitum for 8 days (dose of 12 mg/kg bw) minimum and maximum blood concentration in steady state ($C_{\min-ss}$ – $C_{\max-ss}$) was 0.3 and 0.75 µg/ml respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Shelled almond flour
Almond shell
Soybean Oil refined
Silica colloidal anhydrous
Apple flavour

6.2 Incompatibilities

In the 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: 2 years
Shelf life after first opening the immediate packaging: 4 months
Shelf life after incorporation into meal or pelleted feed: 4 months

6.4. Special precautions for storage

Store below 25 °C.
Store in the original package in order to protect from light.

6.5 Nature and composition of immediate packaging

25 kg multi-layer paper bag with internal low density polyethylene bag, closed by thermos-sealing.

Package size:
Bag of 25 kg.

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 product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

LABORATORIOS CALIER, S.A.

C/. Barcelonés, 26 (P.I. El Ramassar)

LES FRANQUESES DEL VALLÈS. Barcelona

SPAIN

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: DD/MM/YYYY

10 DATE OF REVISION OF THE TEXT

DD/MM/YYYY

PROHIBITION OF SALE, SUPPLY AND/OR USE

To be supplied only on veterinary prescription

Consideration should be given to official guidance on the incorporation of medicated premixes in final feeds.