SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

KARIDOX 125 mg/g Premix for medicated feeding stuff for pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each g contains:

Active substance:

Doxycycline (hyclate)	125.0 mg
(as doxycycline hyclate	144.2 mg)

Excipients:
Flour of hazelnut and almond shell

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Premix for medicated feeding stuff.
Brown yellowish 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 pleuropneumonia caused by *Actinobacillus pleuropneumoniae* susceptible to doxycycline.
The presence of the disease in the herd should be established before use.

4.3 Contraindications

Do not use in cases of hypersensitivity to tetracyclines or to any of the excipients.
Do not use in animals with hepatic dysfunction.
See section 4.7 “Use during pregnancy, lactation or lay”.

4.4 Special warnings for each target species

The intake of medicated feed by animals can be altered as a consequence of illness. In case of insufficient intake of feed, animals should be treated parenterally.

4.5 Special precautions for use

Special precautions for use in animals

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.

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.

Consideration should be given to improvement of management practices on the farm. Particular attention should be paid to hygiene and ventilation, and management of pigs to avoid stress-related conditions.

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 the 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 the necessary measures to avoid producing dust during the incorporation of the premix into feed.
- Personal protective equipment consisting of an appropriate 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), impermeable gloves, overalls and approved safety goggles should be worn when handling the veterinary medicinal product
- Avoid skin and eye contact. In case of accidental exposure rinse immediately with plenty of water and if irritation occurs, seek medical attention.
- Do not smoke, eat or drink while handling the product.

In case of accidental ingestion or if you develop symptoms following exposure such as skin rash, seek medical immediately and show the package leaflet or the label to the physician. Swelling of the face, lips or eyes or difficulty in breathing are more serious symptoms and require urgent medical attention.

4.6 Adverse reactions (frequency and seriousness)

As for all tetracyclines, on rare occasions allergic reactions and photosensitivity may occur.
In prolonged treatments digestive alterations may appear due to intestinal dysbiosis.

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 reports).

4.7 Use during pregnancy, lactation or lay

Pregnancy:
Laboratory studies in mice and rabbits have not produced any evidence of toxic effects. The safety of the veterinary medicinal product has not been established during pregnancy in sows, the use is not recommended during pregnancy.

Lactation:
The safety of the veterinary medicinal product has not been established during lactation in sows, thus its use is not recommended during lactation.

Fertility:
Do not use in breeding animals.

4.8 Interaction with other medicinal products and other forms of interaction

The absorption of doxycycline can be reduced in the presence of high amounts of Ca^{2+}, Fe^{3+}, Mg^{2+} or Al^{3+} in the diet. Do not administer together with antacids, kaolin and iron preparations and in conjunction with bactericidal antibiotics like beta-lactams.

4.9 Amounts to be administered and administration route

In-feed use.

The premix is administered directly mixed with feed according to the following dose:

10-12 mg of doxycycline/kg bodyweight/day, equivalent to 80-95 mg of the product/kg bodyweight/day.

Treatment should be continued for 8 days.

Since the intake of feed will vary depending on the clinical condition of the animals, 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:

$$\text{mg of veterinary medicinal product per kg of feed} = \frac{\text{80 – 95 mg veterinary medicinal product/kg b.w./day x mean body weight (kg) of animals to be treated}}{\text{Mean daily feed intake/animal (kg)}}$$

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

The recommended incorporation rate into feed would be 2 kg of the veterinary medicinal product per tonne of feed.

The required doses should be measured by suitably calibrated weighing equipment.

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

Not described.

4.11 Withdrawal period(s)

Pigs for fattening:
Meat and offal: 5 days

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use. Tetracyclines.
ATCvet code: QJ01AA02.

5.1 Pharmacodynamic properties

Doxycycline is a bacteriostatic antibacterial agent that acts by interfering with bacterial protein synthesis of susceptible species.

Doxycycline is a semisynthetic tetracycline derivative from oxytetracycline. It acts on the 30S ribosomal subunit of bacteria by reversible binding. This binding blocks the union between tRNA-

aminoacyl (transfer RNA) and the complex of mRNA and ribosomes. This avoids the addition of new amino acids to the peptide chain, thus, it inhibits the protein synthesis.

It acts against gram-positive and gram-negative bacteria, particularly on *Actinobacillus pleuropneumoniae.*

Critical concentrations (breakpoints) of sensitive (S) or resistance (R) in µg/ml of tetracycline: (Source: CLSI 2008)

	S		**R**
Bacteria different from streptococci	≤ 4	8	≥ 16

There are at least two resistance mechanisms to tetracyclines. The most important mechanism is due to a decrease in the intracellular accumulation of the drug. It is due to an elimination route by antibacterial efflux or due to an alteration in the transport, decreasing the tetracycline uptake dependent on energy from the outside of the cell. The alteration in the transport is due to inducible proteins which are codified by plasmids and transposons.

The other mechanism is observed by a decrease in the affinity between the ribosome and the Tetracycline-Mg^{2+} complex due to mutations on the chromosome.

There is cross-resistance between tetracyclines.

5.2 Pharmacokinetic particulars

The absorption after oral administration is high (67 %). The food intake could modify the oral bioavailability of doxycycline. In a fasting state the bioavailability is 10-15 % higher than when the animal ingests food.

The doxycycline is widely distributed in the organisms due to its physico-chemical characteristics, because it is highly liposoluble. At steady state, the volume of distribution (V_{SS}) is 0.97 L/kg. Doxycycline reaches well-perfused and peripheral tissues. Doxycycline is concentrated in the liver, kidneys, bones and gut. In this last case it is because doxycycline undergoes enterohepatic circulation. Doxycycline reaches higher concentrations in the lungs than in plasma.

40 % of the drug is metabolized and widely excreted by faeces (intestinal and biliary route). The major part is excreted as inactive microbiologically conjugates.

SWINE
The binding rate to plasma proteins is 93% for doxycycline in pigs. The AUCss following repeated oral administration in feed (15 administrations at the mean dosage regimen of 5.9 ± 0.3 mg/kg/12 h) was 10.92 ± 2.17 µg•h/ml.

After administration of one dose of 10 mg/kg b.w. in feed, the maximum plasma concentration was 1.5 µg/ ml and it was reached between 6 and 8 hours after administration. The plasma elimination half-life was 23.54 h.

After administration of medicated feed with 250 mg of doxycycline/kg of feed, administered *ad libitum* for 8 consecutive days (dose rate of 12 mg/kg b.w.), the minimum and maximum plasma concentrations at steady state (Css_{min} – Css_{max}) were 0.3 and 0.75 µg/ml respectively.

The clearance was determined to be 173 ± 66.5 mL/h.kg after oral administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Flour of hazelnut and almond shell
Propylene glycol

6.2 Major 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: 2 months
Shelf life after incorporation into meal or pelleted feed: 1 month

6.4. Special precautions for storage

Do not store above 30 ºC.
Keep the bags tightly closed in order to protect from light and to avoid the introduction of contamination.

6.5 Nature and composition of immediate packaging

Kraft paper bags of three ply with an inner layer of Low Density Polyethylene.

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

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8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:
Date of last renewal:

10 DATE OF REVISION OF THE TEXT

February 2020

PROHIBITION OF SALE, SUPPLY AND/OR USE

Consideration should be given to official guidance on the incorporation of medicated premixes in final feeds.
To be supplied only on veterinary prescription.
To be administered by the veterinarian or under veterinarian supervision.