SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Doxyveto 500 mg/g powder for use in drinking water/milk replacer for cattle, pig, chicken

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Per 1 gram:

Active substance:
Doxycycline hyclate 500 mg, equivalent to 433 mg doxycycline

Excipients:
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for use in drinking water/milk replacer
Fine yellow, homogeneous powder.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle (pre-ruminating calf), pig, chicken (broilers, breeders, replacement chicks).

4.2 Indications for use, specifying the target species

Treatment of below mentioned infections of the respiratory and gastrointestinal tract caused by micro-organisms sensitive to doxycycline.

Pre-ruminant calves:
- Bronchopneumonia and pleuropneumonia caused by *Pasteurella spp, Streptococcus spp, Trueperella pyogenes, Histophilus somni* and *Mycoplasma spp.*.

Pigs:
- Atrophic rhinitis caused by *Pasteurella multocida* and *Bordetella bronchiseptica*;
- Bronchopneumonia caused by *Pasteurella multocida, Streptococcus suis* and *Mycoplasma hyorhinis*;
- Pleuropneumonia caused by *Actinobacillus pleuropneumoniae*.

Chickens:
- Respiratory infections caused by *Mycoplasma spp, Escherichia coli, Haemophilus paragallinarum* and *Bordetella avium*;
- Enteritis caused by *Clostridium perfringens* and Clostridium colinum.

4.3 Contraindications

Do not use in cases of hypersensitivity to tetracyclines or to any of the excipients.
Do not use in animals with serious liver or kidney deficiency.
Do not use in ruminating cattle.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals

As a result of a likely variation (in the course of time or geographically) in the susceptibility of bacteria to doxycycline, bacteriological testing and susceptibility testing of micro-organisms from diseased animals on a farm is strongly recommended.

There is a high resistance rate documented against tetracyclines in *E. coli* isolated from chickens. Therefore the product should only be used for the treatment of infections caused by *E. coli* after susceptibility testing has been carried out. Resistance to tetracyclines has also been reported in some EU countries in pathogens of pigs (*A. pleuropneumoniae, S. suis*) and pathogens of calves (*Pasteurella spp*.).

As complete elimination of the target pathogens may not be achieved, the medicinal product should be combined with good management practices, such as good hygiene, proper ventilation and no overstocking.

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

- This product may cause contact dermatitis and/or hypersensitivity reactions if contact is made with the skin or eyes (powder and solution), or if the powder is inhaled.
- People with known hypersensitivity to tetracyclines should not handle the product. 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.
- Do not smoke, eat or drink while handling 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.

4.6 Adverse reactions (frequency and seriousness)

As for all tetracyclines, adverse reactions may occur, such as gastrointestinal disturbances and, on rare occasions, allergic reactions and photosensitisation. If suspected adverse reactions occur, treatment should be discontinued.

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

Laboratory studies in rats and rabbits have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects.
The safety of the veterinary medicinal product has not been established in pregnant or lactating sows. The use is not recommended during pregnancy or lactation.

4.8 Interaction with other medicinal products and other forms of interaction

Not to be administered in combination with bactericidal antibiotics, such as penicillins and cephalosporins.
Tetracyclines may chelate cations (eg. Mg, Mn, Fe and Al) and this can lead to reduced bioavailability.
The combination with mycotoxin-binding agents can lead to both increased and decreased plasma concentrations of doxycycline and should therefore be avoided.
The presence of food in the gastrointestinal tract reduces the likelihood of such interactions.

4.9 Amounts to be administered and administration route

Oral administration, via the drinking water/milk replacer

Pre-ruminating calves:	10 mg doxycycline hyclate/kg bw/day, equivalent with 20 mg product per kg bw during 3-5 consecutive days. The daily dose should be given in 2 administrations.
Pigs:	10 mg doxycycline hyclate/kg bw/day, equivalent with 20 mg product per kg bw, during 3-5 consecutive days.
Chickens:	25 mg doxycycline hyclate/kg bw/day, equivalent with 50 mg product per kg bw, during 3-5 consecutive days.

For administration via the drinking water/milk replacer, the exact daily dose of the product is to be calculated, based on above mentioned recommended dose and the number and weight of the animals to be treated using the following formula:

$$\frac{\text{mg product / kg bw / day} \times \text{average bw (kg) of the animals to be treated}}{\text{mean daily water / milk consumption (litre) per animal}}$$

= … mg product per litre drinking water/milk replacer

To ensure a correct dosage, body weight should be determined as accurately as possible.
The uptake of medicated water/milk replacer depends on the clinical condition of the animals. In order to obtain the correct dosage, the concentration in the drinking water/milk replacer possibly needs to be adjusted.
A calibrated weighing device should be used in order to obtain proper dosages.
The daily amount is to be added to the drinking water in such manner that all medication is taken up in 24 hours. Medicated drinking water should be freshly prepared every 24 hours. Half the daily amount is to be added to milk replacer in such manner that all medication is taken up in 2 hours. It is recommended to prepare a concentrated stock solution - not exceeding 150 grams product per litre drinking water - and to dilute this further to therapeutic concentrations if required. Instead, the concentrated solution may also be used in a water-driven medicator for proportional administration. Milk replacer: half the daily amount is to be added to milk replacer in such manner that all medication is taken up in 2 hours.

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

In calves, acute and sometimes fatal myocardial degeneration following a single or repeated administration may occur. Since this is often caused by overdosing, it is important to accurately weigh the dosage.

4.11 Withdrawal period(s)

Calves
Meat and offal: 7 days
Not authorised for use in animals producing milk for human consumption.

Pigs
Meat and offal: 8 days

Chicken
Meat and offal: 5 days
Not for use in birds producing or intended to produce eggs for human consumption.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibiotic for systemic use, tetracyclines.
ATC vet code: QJ01AA02.

5.1 Pharmacodynamic properties

Doxycycline is a broad spectrum antibiotic. It inhibits bacterial protein synthesis intracellularly by binding to the 30S ribosomal subunits. The entry of aminoacetyl-tRNA to the acceptor site on the mRNA ribosome complex is blocked in this manner, whereby coupling of the amino acids to the forming peptide chain is prevented. Doxycycline inhibits bacteria, Mycoplasmata, Chlamydia, Rickettsia, and certain protozoa.
In general, four resistance mechanisms against tetracyclines obtained by micro-organisms have been reported: reduced accumulation of tetracyclines (reduced permeability of the bacterial cell wall and active efflux), protein protection of the

bacterial ribosome, enzymatic inactivation of the antibiotic and rRNA-mutations (which prevents the binding of tetracycline to the ribosome). Resistance to tetracycline is usually obtained via plasmids or other mobile elements (eg. conjugative transposons). Cross resistance between tetracyclines has also been described. Because of the greater lipid solubility and improved ability to cross cell membranes (as compared to tetracycline), doxycycline retains a certain level of activity against micro-organisms with an acquired resistance to tetracyclines.

5.2 Pharmacokinetic particulars

Doxycycline is quickly and almost completely absorbed from the intestine. Presence of food in the intestine has no effect on the actual absorption of doxycycline. The distribution of doxycycline in the body and the penetration in most tissues is good. Following absorption, tetracyclines are hardly metabolized. Doxycycline is unlike other tetracyclines mainly excreted in the faeces.

Calves
After a dose of 10 mg / kg body weight / day for 5 days, an elimination half-life was found ranging from 15 to 28 hours. The doxycycline plasma level reached a mean of 2.2 to 2.5 µg / ml.

Pigs
In pigs, no accumulation of doxycycline was found in plasma after treatment via the drinking water. Mean plasma levels of 0.44 ± 0.12 µg / ml were found after 3 days of medication with a mean dose of 10 mg / kg body weight.

Chickens
Steady state plasma concentrations of 2.05 ± 0.47 µg / ml were reached within 6 hours after the start of the medication and varied between 1.28 and 2.18 µg / ml with a dose of 25 mg / kg body weight for 5 days.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid, anhydrous.
Lactose monohydrate.

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

Bag
Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after first opening the immediate packaging: 3 months.
Shelf life after reconstitution in water according to directions: 24 hours.
Shelf life after reconstitution in milk replacer according to directions: 2 hours.

Jar
Shelf life of the veterinary medicinal product as packaged for sale: 3 years
Shelf life after first opening the immediate packaging: 3 months.
Shelf life after reconstitution in water according to directions: 24 hours.
Shelf life after reconstitution in milk replacer according to directions: 2 hours.

6.4 Special precautions for storage

Bag:
Store below 25 °C.
Tightly reclose the bags after first opening in order to protect from light.
Protect the medicated drinking water from direct sunlight.

Jar:
Store below 25 °C.
Tightly reclose the jars after first opening in order to protect from light.
Protect the medicated drinking water from direct sunlight.

6.5 Nature and composition of immediate packaging

Multi-layer laminated bags (polyester/aluminium/polyethylene) containing 1 kg.
Polyethylene jars with polypropylene lid with a carton/aluminium/polyethylene inner-layer containing 100 g or 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 product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

Vm 19968/4005

9. DATE OF FIRST AUTHORISATION

29 January 2018

10. DATE OF REVISION OF THE TEXT

21 June 2022

PROHIBITION OF SALE, SUPPLY AND/OR USE

On veterinary prescription.

Approved 21 June 2022