Summary of Product Characteristics

1 NAME OF THE VETERINARY MEDICINAL PRODUCT

Doxipulvis 500 mg/g powder for use in drinking water / milk replacer

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains:
Active substance:

Doxycycline 500.0 mg
(As doxycycline hyclate 577.1 mg)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for use in drinking water / milk replacer

Yellow fine powder

4 CLINICAL PARTICULARS

4.1 Target Species

Cattle (pre-ruminant calves), pigs, chickens (broilers, breeders) and turkeys (broilers, breeders)

4.2 Indications for use, specifying the target species

In calves:
- Treatment and metaphylaxis of respiratory and digestive infections caused by micro-organisms susceptible to doxycycline.

In pigs:
- Treatment and metaphylaxis of respiratory infections caused by micro-organisms susceptible to doxycycline.

In chickens and turkeys:
- Treatment and metaphylaxis of respiratory infections due to micro-organisms susceptible to doxycycline.

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

4.3 Contraindications

Do not use in cases of known hypersensitivity to doxycycline other tetracyclines or the excipient.
Do not use in case of known resistance to tetracyclines.
Do not use in animals with renal or hepatic disorders.
Do not use in ruminating animals.

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, calves and pigs should be treated parenterally.

4.5 Special precautions for use

Special precautions for use in animals

Due to the likely variability (time, geographical) in the occurrence of resistance of bacteria for doxycycline, bacteriological sampling and susceptibility testing of micro-organisms form diseased animals are highly recommended.
A high resistance rate for *Escherichia 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. Resistance to tetracyclines has also been reported in pig respiratory pathogens (*Actinobacillus pleuropneumoniae*, *Streptococcus suis*) and calf pathogens (*Pasteurella* spp.) in some EU countries.
Official and local antimicrobial policies should be taken into account when the product is used.
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 other tetracyclines due to the potential for cross-resistance.
As the eradication of target pathogens may not be achieved, medication should therefore be combined with good animal management practices e.g. good hygiene, proper ventilation, no overstocking.

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

People known to be allergic to the tetracycline class of antibiotics, should take special care when handling this product or the medicated solution.
This product may cause contact dermatitis and/or hypersensitivity reactions following skin or eye contact (with the powder or medicated solution), or if the powder is inhaled.
Take measures to avoid producing dust when incorporating the product into water.

During preparation and administration direct contact of the product with the skin, eyes and mucous membranes and inhalation of dust particles should be avoided.
Wear impervious gloves (e.g. rubber or latex), safety glasses and an appropriate dust mask (either a disposable half-mask respirator conforming to European Standard EN149) or a non-disposable respirator to European Standard EN 140 with a filter to EN 143), when handling the product.
In the event of eye or skin contact, rinse the affected area with plenty of clean water.
If symptoms develop following exposure, such as skin rash, seek medical advice and show this warning to the physician. Swelling of the face, lips or eyes or difficulty breathing are more serious symptoms and require urgent medical attention.
Do not smoke, eat or drink while handling the product.
Wash hands and contaminated skin immediately after handling the product.

4.6 Adverse reactions (frequency and seriousness)

As for all tetracyclines, adverse reactions may occur, such as gastrointestinal disturbances and, with lower frequency, allergic reactions and photosensitisation.
If suspected adverse reactions occur, treatment should be discontinued.

4.7 Use during pregnancy, lactation or lay

Doxycycline showed no evidence of teratogenic or embryotoxic effects in laboratory animals.
In mammals, doxycycline crosses the placental barrier. Due to a lower affinity for calcium, doxycycline results in less staining of teeth compared to tetracycline. Doxycycline is found in breast milk.
The safety of the veterinary medicinal product has not been established during pregnancy and lactation. In pregnant and lactating animals use only accordingly to the benefit-risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

Divalent or trivalent cations (Mg, Fe, Al, Ca) can chelate tetracyclines. Tetracyclines should not be administered with antiacids, gels based on aluminum, preparations based on vitamins or minerals, since insoluble complexes are formed, which reduces the absorption of the antibiotic.
Do not use in conjunction with bactericidal antibiotics, such as penicillins or cephalosporins.
Doxycycline increases the action of anticoagulants.

4.9 Amounts to be administered and administration route

To be administered orally in milk replacer, drinking water or liquid feed.

Calves, pigs:

10 mg of doxycycline per kg of body weight per day (equivalent to 11.54 mg of doxycycline hyclate/kg bw /day), during 3 to 5 days, or 0.2 g of powder per 10 kg of body weight per day, during 3-5 consecutive days, to be dissolved in drinking water, milk replacer or liquid feed; to be adjusted according to actual feed intake of the animals, in order to meet the weight dosage.

Chickens and turkeys:

10 mg of doxycycline per kg of body weight per day (equivalent to 11.54 mg of doxycycline hyclate/kg bw /day), equivalent to 0.02 g of soluble powder per kg of body weight during 3 to 5 consecutive days, to be dissolved in drinking water.

The exact daily amount of oral powder based on the recommended dose and the number and weight of the animals to be treated should be calculated according to the following formula:

$$\frac{\text{0.02 g of powder per kg of body weight per day} \times \text{body weight (kg) of the animals to be treated}}{\text{Average water intake per animal (litres)}} = \ldots \text{ g of powder per litre of drinking water}$$

To ensure accuracy of the dose, the body weight should be determined as precisely as possible.

The intake of water containing the drug substance depends on the clinical condition of the animals. To obtain the correct dose, it may be necessary to adjust the concentration in the drinking water.

The use of suitably calibrated weighing equipment is recommended if part packs are used. The daily amount of powder should be added to the drinking water so that the drug is consumed in 24 hours divided in two administrations. Drinking water containing the drug substance has to be freshly prepared every 12 hours. It is recommended to prepare a concentrated solution (approximately 10 g of product per litre of water) which can be diluted later, if necessary, to the therapeutic concentration. It is also possible to distribute the concentrated solution using a metering pump.

The product should not be prepared at a concentration below 0.1 g of powder/L of hard water/ milk replacer and at pH above 8.2.
The solubility of the product has been tested at the maximum concentration of 400 g/L.

The medicated water should be the only source of drinking water, throughout the treatment period. Water uptake should be monitored at frequent intervals during medication.
Sufficient access to the system of water supply should be available for the animals to be treated to ensure adequate water consumption. The medicated water must not be prepared or stored in a metal container. After the end of the medication period, the water supply system should be cleaned appropriately to avoid intake of sub-therapeutic amounts of the active substance.

The temperature of the milk replacer should not be above 38 ºC prior to the introduction of the finished product. The medicated milk replacer should be used immediately and should be freshly prepared after 1 hour at the latest.

When administering in liquid feed, first dissolve the product in water and then add feed. The preparation should be used immediately. Care should be taken that the intended dose will be completely ingested.

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

Not described. If suspected toxic reactions occur, the medication should be discontinued and appropriate symptomatic treatment should be initiated.

4.11 Withdrawal Period(s)

Meat and offal:

- Calves: 14 days
- Pigs: 6 days
- Chicken: 7 days
- Turkeys: 12 days

Eggs: Not authorized for use in laying birds producing eggs for human consumption. Do not use within 4 weeks of onset of the laying period.

5 PHARMACOLOGICAL or IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: antibiotic for systemic use, tetracycline.
ATCvet code: QJ01AA02

5.1 Pharmacodynamic properties

Doxycycline binds reversibly to receptors of ribosomal fraction 30S, which leads to a blockade of the aminoacyl-tRNA binding to the corresponding site of the complex ribosome-RNA messenger. This results in inhibition of protein synthesis and therefore stops the growth of the bacterial culture. Doxycycline has a predominantly bacteriostatic activity.

The bacteriostatic activity of doxycycline involves penetration of the substance into the bacterial cell. The penetration of doxycycline takes place by both active and passive diffusion. The main resistance mode is related to the possible presence of an R factor responsible for a decrease in the active transport of doxycycline.

Doxycycline is a broad spectrum antibiotic. It is primarily active against Gram positive and negative microorganisms, aerobic and anaerobic, and against *Mycoplasma*, *Chlamydia* and *Rickettsiae*.

Cross-resistance to other tetracyclines may occur. Usually such resistance has a plasmid origin. A continuous treatment with low doses of doxycycline may also result in an increased resistance to other antibiotics.

The following Minimal Inhibitory Concentrations (MIC) have been determined for doxycycline in European isolates target pathogens:

Species	**Bacterial pathogen**	**Year of sampling**	**MIC_{50} (mcg/ml)**	**MIC_{90} (mcg/ml)**
Chickens /Turkeys	*M gallisepticum*	2001	0.006-0.12	
	M synoviae	2001 - 2004	0.015-0.03	
Pigs	*A.pleuropneumoniae*	2002-2014	0.25-2	1
	P. multocida	2005-2014	0.12-0.5	2
Ruminants	*P. multocida*	2002-2006	0.25	0.5
	M. haemolytica	2002-2006	0.25	2

5.2 Pharmacokinetic properties

Doxycycline is quickly (2 - 3 hours) absorbed after oral administration and its bioavailability in most species is around 70 %.

Doxycycline is highly bound to plasma proteins (about 90 %). Highly fat soluble in comparison to first generation tetracyclines, doxycycline is widely distributed throughout the body. The highest concentrations were found in the lungs, kidneys, liver and spleen. Doxycycline crosses the placental barrier.

Doxycycline is excreted by the biliary route, but a large proportion is reabsorbed by the small intestine (enterohepatic cycle). 40 % of doxycycline is metabolized and excreted in the feces, mainly as inactive conjugated metabolites.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid anhydrous

6.2 Incompatibilities

In the absence of compatibility studies, this 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: 1 month
Shelf life after dilution in drinking water according to directions: 12 hours
Shelf life after dilution in milk replacer according to directions: 1 hour
Shelf life after dilution in liquid feed according to directions: use immediately

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

Low-density polyethylene/ Aluminium/ Polypropylene bags containing 200 g or 1 kg of powder.
Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal products or waste materials

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

SP VETERINARIA SA
Ctra Reus Vinyols km 4.1
Riudoms (43330)
Spain

8 MARKETING AUTHORISATION NUMBER(S)

VPA 10790/008/001

9 DATE OF THE FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30th September 2016

10 DATE OF REVISION OF THE TEXT