Summary of Product Characteristics

1 NAME OF THE VETERINARY MEDICINAL PRODUCT

Doxatib 500 mg/g powder for use in drinking water for pigs and chickens

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each g of powder contains:

Active substance:
Doxycycline hyclate 500 mg
(corresponding to 433 mg of doxycycline)

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

3 PHARMACEUTICAL FORM

Powder for use in drinking water.
Pale yellow to yellow powder.

4 CLINICAL PARTICULARS

4.1 Target Species

Pigs and chickens (broilers, pullets, broiler breeders).

4.2 Indications for use, specifying the target species

Pigs: For the treatment of the clinical signs associated with porcine respiratory disease caused by *Actinobacillus pleuropneumoniae, Pasteurella multocida* and *Mycoplasma hyopneumoniae* susceptible to doxycycline.

Chickens: Where clinical disease is present in the flock, to reduce mortality, morbidity, and clinical signs and to reduce lesions due to Pasteurellosis caused by *Pasteurella multocida* or to reduce morbidity and lesions in respiratory infections caused by *Ornithobacterium rhinotracheale* (ORT).

4.3 Contraindications

Do not use in known cases of hypersensitivity to tetracyclines or to any of the excipients.
Do not use in animals with an impaired liver function.
Do not use in animals with renal disorders.
Do not use when tetracycline resistance has been detected in the herd/flock due to the potential for cross resistance.

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, animals should be treated parenterally.

4.5 Special precautions for use

Special precautions for use in animals
Official, national and regional 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.
Resistance to tetracyclines has also been reported in pig respiratory pathogens (*A. pleuropneumoniae*) in some EU countries.

Due to likely variability (time, geographical) in the occurrence of resistance of bacteria against doxycycline bacteriological sampling and susceptibility testing are recommended. In particular susceptibility of *A. pleuropneumoniae* and *O. rhinotracheale* may differ from country to country and even farm to farm. 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.
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.

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 avoid contact with the veterinary medicinal 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.
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 or a non-disposable respirator to European Standard EN140 with a filter to EN143) when mixing and 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.
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.
Wash hands after handling the product.
Do not smoke, eat or drink while handling the product.

4.6 Adverse reactions (frequency and seriousness)

Tetracyclines may - in very rare cases - induce photosensitivity and allergic reactions. 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

Doxycycline has a low affinity for forming complexes with calcium and studies have demonstrated that doxycycline scarcely affects skeleton formation.
In the absence of specific studies the use of the product is not recommended during pregnancy or lactation.

4.8 Interaction with other medicinal products and other forms of interactions

Do not combine with antibiotics that are bactericidal e.g. penicillins or cephalosporins.
Absorption of doxycycline can be decreased in the presence of high quantities of calcium, iron, magnesium or aluminium in the diet. Do not administer concurrently with antacids, kaolin and iron preparations.
It is advised that the interval between the administration of the product and administration of other products containing polyvalent cations should be 1-2 hours because the latter limit the absorption of tetracyclines.
Doxycycline increases the action of anticoagulants.

4.9 Amounts to be administered and administration route

In drinking water use:

Pigs: the recommended dose is:
12.5 mg doxycycline hyclate (25 mg product) per kg body weight per day for 4 consecutive days.

If no improvement in clinical signs is seen within this time, the diagnosis should be reviewed and treatment changed. In case of severe infections the medication period may be prolonged for a maximum of 8 consecutive days as determined by the attending veterinary surgeon.

Chickens: the recommended dose is:
10 mg doxycycline hyclate (20 mg product) per kg body weight per day for 3 - 4 consecutive days in case of infections caused by *P. multocida* and
20 mg doxycycline hyclate (40 mg product) per kg body weight per day for 3 - 4 consecutive days in case of infections caused by *O. rhinotracheale*.

Based on the dose to be used, and the number and weight of the animals to be treated, the exact daily amount of product can be calculated. The following formula can be used to calculate the concentration of the product in drinking water:

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

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

The intake of medicated drinking water depends on the clinical condition of the animals. In order to obtain the correct dosage, the concentration of doxycycline has to be adjusted accordingly.

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 replaced 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.

Solubility of the product is pH dependent and it may precipitate if it is mixed in hard alkaline drinking water. Use at minimum concentrations of 200 mg powder per litre drinking water in areas with hard alkaline drinking water (hardness above 10.2 °d and pH more than 8.1).
Do not store the drinking water in metallic containers.

It should be ensured that all animals intended for treatment should have free access to the drinking facilities.
During the treatment period animals should not have access to other water sources than the medicated water.

Water uptake should be monitored at frequent intervals during medication.
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.

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

Overdoses up to 1.6 times the label recommended dose resulted in no clinical signs that could be attributed to treatment. Poultry tolerate double overdoses of doxycycline (40 mg/kg body weight) without any clinical effect.

4.11 Withdrawal period(s)

Pigs:
- Meat and offal: 4 days

Chickens:
- Meat and offal: 3 days (following a dose rate of 10 mg/kg body weight for 4 days).
- Meat and offal: 9 days (following a dose rate of 20 mg/kg body weight for 4 days).
- Eggs: Not authorised 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: Antibacterial for systemic use, Tetracyclines.
ATCvet code: QJ01AA02

5.1 Pharmacodynamic properties

Doxycycline belongs to the group of the tetracycline antibiotics. These antibiotics share the same basic structure of polycyclic naphthacenecarboxamide.
Doxycycline is primarily a bacteriostatic drug. It exerts its action by inhibiting the protein synthesis of the bacterial cell. Inhibition of bacterial protein synthesis results in disturbance of all functions necessary for the life of bacteria. In particular, cell-division and the formation of the cell wall are impaired.
Doxycycline is a broad-spectrum antibiotic, active against a large number of Gram-positive and Gram-negative, aerobic and anaerobic micro-organisms and Mycoplasmas.
For *Ornithobacterium rhinotracheale* results demonstrate a great variation from high to low susceptibility, depending on the geographical region where isolates came from.
In pig pathogens resistance against doxycycline may also vary; in particular susceptibility figures of *A. pleuropneumoniae* may differ from country to country and even farm to farm.
Four resistance mechanisms acquired by microorganisms against tetracyclines in general have been reported: decreased accumulation of tetracyclines (decreased permeability of the bacterial cell wall and active efflux), protein protection of the bacterial ribosome, enzymatic inactivation of the antibiotic and rRNA mutations (preventing the tetracycline binding to ribosome). Tetracycline resistance is usually acquired by means of plasmids or other mobile elements (e.g. conjugative transposons). Cross resistance between tetracyclines is common but depends on the mechanism conferring resistance. Due to the greater liposolubility and greater ability to pass through cell membranes (in comparison to tetracycline), doxycycline retains a certain degree of efficacy against microorganisms with acquired resistance to tetracyclines via efflux pumps. However, resistance mediated by ribosomal protection proteins confer cross-resistance to doxycycline.

5.2 Pharmacokinetic particulars

Doxycycline is absorbed in the stomach and the first part of the duodenum. Compared to the older tetracyclines the absorption of doxycycline is less affected by the presence of bivalent cations in food. Bioavailability in non-fasted pigs is approximately 21 %.
Following oral administration at a dose of 12.8 mg/kg body weight, steady state concentrations during medication range between a C_{min} of 0.40 µg/ml in the early morning to a C_{max} of 0.87 µg/ml in the late afternoon in pigs.
Following administration of doxycycline hyclate at an actual dose of 21 mg/kg body weight to chickens mean plasma concentrations above 1 µg/ml were reached within 6 hours and lasted for 6 hours after cessation of medication. From 24 h up to 96 h after start of treatment the doxycycline plasma concentrations exceeded 2 µg/ml. Following administration of doxycycline hyclate at an actual dose of 10 mg/kg body weight steady state plasma concentrations ranged from 0.75 to 0.93 µg/g between 12 and 96 hours after start of medication.
Because doxycycline is highly lipid soluble, it has a good tissue penetration. Respiratory tract tissue: plasma ratios of 1.3 (healthy lungs), 1.9 (pneumonic lungs) and 2.3 (nasal mucosa) have been reported for doxycycline. Plasma protein binding is high (over 90 %).
Doxycycline is scarcely metabolised. Doxycycline is primarily excreted with the faeces.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tartaric acid

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: 1 year
Shelf life after dilution or reconstitution according to directions: 24 hours

6.4 Special precautions for storage

Store below 30 °C.
Store in the original package.
Keep the bag tightly closed after first opening in order to protect from moisture.
Once opened, the veterinary medicinal product should be stored at temperatures below 25 °C.

6.5 Nature and composition of immediate packaging

Alu triplex (PET/Al/PE) bags.
Alu quadriplex (PET/Al/PET/PE) bags.
Pack sizes of 100 g, 1 kg and 5 kg.

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal products 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

Krka, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8 MARKETING AUTHORISATION NUMBER(S)

VPA10774/046/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 September 2016
Date of last renewal: 02 July 2021

10 DATE OF REVISION OF THE TEXT

July 2021