1 NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g powder contains:

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

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

3 PHARMACEUTICAL FORM

Powder for use in drinking water.
Yellow crystalline powder.

4 CLINICAL PARTICULARS

4.1 Target Species

Pigs and chickens (broiler, pullet, breeder).

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, clinical signs and to reduce lesions due to Pasteurellosis caused by *Pasteurella multocida*, or to reduce morbidity and lesions due to respiratory infections caused by *Ornithobacterium rhinotracheale* (ORT).

4.3 Contraindications

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.
Do not use in animals with an impaired liver function.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals
Due to likely variability (time, geographical) in susceptibility of bacteria to doxycycline, especially susceptibility of A. *pleuropneumoniae* and O. *rhinotracheale* which may differ from country to country and even farm to farm, bacteriological sampling and susceptibility testing are recommended. Use of the product should be based on the culture and sensitivity of micro-organisms from diseased cases on farms. 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
If you know you are allergic to the tetracycline class of antibiotics, special care should be taken when handling this product or the medicated solution.
During preparation and administration of the medicated drinking water, skin contact with the product and 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) when 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. 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.
Do not smoke, eat or drink while handling the 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.

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. Inform your veterinary surgeon if adverse reactions occur that are not stated.

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. No negative effects were observed in poultry after the administration of therapeutic doses of doxycycline.
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 interaction

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 together with antacids, kaolin and iron preparations.
It is advised that the interval between the administration of other products containing polyvalent cations should be 1-2 hours because they limit the absorption of tetracyclines.
Doxycycline increases the action of anticoagulants.
The solubility of the product is pH dependent and it will precipitate if mixed in alkaline solution.
Do not store the drinking water in metallic containers.

4.9 Amounts to be administered and administration route

Administration orally with the drinking water.

The recommended dose in pigs 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.

The recommended dose in *chickens* 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 daily amount of product required can be calculated. The following formula can be used to calculate the concentration of the product required in drinking water:

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

To ensure a correct dosage body weight should be determined as accurately as possible. The uptake of medicated drinking water depends on the clinical condition of the pigs/chickens. 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 of product required is to be added to the drinking water such that all medication will be consumed in 24 hours. Medicated drinking water should be refreshed or 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 out 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). During the treatment period animals should not have access to water sources other than the medicated water.

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.
Not authorised for use in birds producing eggs for human consumption.
Do not use within 4 weeks of onset of laying.

5 PHARMACOLOGICAL or IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterial - Tetracycline.
ATCvet code: QJ 01 AA 02

5.1 Pharmacodynamic properties

Doxycycline belongs to the group of the tetracycline antibiotics. These antibiotics have a broad-spectrum of antimicrobial activity, sharing 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. Cell-division and the formation of the cell wall in particular are impaired.
Doxycycline is a broad-spectrum antibiotic, active against a large number of Gram-positive and Gram-negative, aerobe and anaerobe micro-organisms, Mycoplasmata, Chlamydiae and Rickettsiae.
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 to 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 micro-organisms 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 has also been described. Due to the greater liposolubility and greater facility to pass through cell membranes (in comparison to tetracycline), doxycycline retains a certain degree of efficacy against micro-organisms with acquired resistance to tetracyclines.

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 hours up to 96 hours 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: 3 years.
Shelf life after first opening the immediate packaging: 9 months.
Shelf life after dilution or reconstitution according to directions: 24 hours.

6.4 Special precautions for storage

Keep the bag tightly closed after first opening in order to protect from moisture.

6.5 Nature and composition of immediate packaging

The packs consists of one of the following laminates:

- Polyester / polyethylene / aluminium / polyethylene and an inner layer of polyethylene.
- Polyester / polyethylene / aluminium and an inner layer of ionomer (surlyn).
- Polyethylene terephtalic acid / aluminium / polyamide and an inner layer of polyethylene.

Pack sizes of 100 g, 250 g, 500 g, 1 kg and 10x100 g in a carton box.
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

Eurovet Animal Health B.V.
Handelsweg 25
5531 AE Bladel
Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

VPA10989/072/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9th February 2018

10 DATE OF REVISION OF THE TEXT