Summary of Product Characteristics

1 NAME OF THE VETERINARY MEDICINAL PRODUCT

Doxylin, 433 mg/g, powder for use in drinking water for chickens and turkeys

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram contains:

Active substance:

Doxycycline:	433.3 mg
(as doxycycline hyclate	500.0 mg)

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

Chickens (broilers, broiler breeders) and turkeys (broilers, breeders).

4.2 Indications for use, specifying the target species

Treatment of clinical respiratory infections associated with *Mycoplasma gallisepticum* susceptible to doxycycline.

4.3 Contraindications

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.
Do not use when tetracycline resistance has been detected in the herd/flock due to the potential for cross resistance.
Do not use in animals with hepatic dysfunction.

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

Due to variability (time, geographical) in susceptibility of bacteria for doxycycline, bacteriological sampling and susceptibility testing of micro-organisms from diseased animals on farm are highly recommended.
Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to doxycycline and may decrease effectiveness of treatment with tetracyclines due to the potential for cross resistance.
Use of the product should take into account official and local antimicrobial policies.
Avoid administration in oxidized drinking equipment.
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

During preparation and administration direct contact of the product with the skin, eyes and mucous membranes and inhalation of dust particles should be avoided.
People with known hypersensitivity to tetracyclines should avoid contact with the veterinary medicinal product.
Wear protective gloves (e.g. rubber or latex), glasses 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 reconstituting or administering the solution. Wash exposed skin after preparation of medicated drinking water. In case of accidental eye contact, rinse with plenty of fresh water. Do not smoke, eat or drink when handling the product.
In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
Inflammation of the face, lips or eyes or respiratory difficulties are the most serious signs which require urgent medical attention.

4.6 Adverse reactions (frequency and seriousness)

As for all tetracyclines, on rare (more than 1 but less than 10 animals in 10,000 animals treated) occasions allergic reactions and photosensitivity may occur. If suspected adverse reactions occur, treatment should be discontinued.

4.7 Use during pregnancy, lactation or lay

Laboratory studies in rats and rabbits have not produced any evidence of a teratogenic, foetotoxic, maternotoxic effects.

4.8 Interaction with other medicinal products and other forms of interactions

Do not administer concurrently with feed overloaded with polyvalent cations such as Ca^{2+}, Mg^{2+}, Zn^{2+} and Fe^{3+} because the formation of doxycycline complexes with these cations is possible. Do not administer together with antacids, kaolin and iron preparations as tetracyclines are bacteriostatic antimicrobials, do not administer in conjunction with bactericidal antibiotics like beta-lactams. It is advised that the interval between administration of other products containing polyvalent cations should be 1-2 hours because they limit the absorption of tetracycline.
Doxycycline increases the action of anticoagulants.

4.9 Amounts to be administered and administration route

To be administered in drinking water.

Dosage:

In chickens
20 mg doxycycline per kg of body weight daily (equivalent to 46 mg product per kg of body weight), administered in the drinking water for 5 consecutive days.

In turkeys
25 mg doxycycline per kg of body weight daily (equivalent to 58 mg product per kg of body weight), administered in the drinking water for 5 consecutive days.

Administration:
Based on the recommended dose, and the number and weight of the animals to be treated, the exact daily amount of product should be calculated according to the following formula:

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

To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing.
The uptake of medicated water is dependent on the clinical conditions of the animals. In order to obtain the correct dosage, the concentration in drinking water may have to be adjusted. 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 freshly prepared every 24 hours. It is recommended to prepare a concentrated pre-solution - not exceeding 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.
It should be ensured that all animals intended for treatment should have free access to the drinking facilities. At the end of treatment, the watering equipment should be cleaned adequately to avoid the uptake of remaining quantities in sub-therapeutic doses. The medicated water should be the only source of drinking water, throughout the treatment period.
The medicated water must not be made or stored in a metal container. Solubility of the product is pH dependent and it will precipitate if it is mixed in an alkaline solution. In order to ensure a complete and permanent dissolution of the veterinary medicinal product in each water quality, a minimum concentration is required. The minimum concentration in drinking water is 200 mg veterinary medicinal product per litre. Animals requiring a lower concentration should not be treated with the product.

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

To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing.
The uptake of medicated water is dependent on the clinical conditions of the animals. In order to obtain the correct dosage, the concentration in drinking water may have to be adjusted. 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 freshly prepared every 24 hours. It is recommended to prepare a concentrated pre-solution - not exceeding 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.
It should be ensured that all animals intended for treatment should have free access to the drinking facilities. At the end of treatment, the watering equipment should be cleaned adequately to avoid the uptake of remaining quantities in sub-therapeutic doses. The medicated water should be the only source of drinking water, throughout the treatment period.
The medicated water must not be made or stored in a metal container. Solubility of the product is pH dependent and it will precipitate if it is mixed in an alkaline solution. In order to ensure a complete and permanent dissolution of the veterinary medicinal product in each water quality, a minimum concentration is required. The minimum concentration in drinking water is 200 mg veterinary medicinal product per litre. Animals requiring a lower concentration should not be treated with the product.

4.11 Withdrawal period(s)

Meat and offal:
Chickens: 5 days.
Turkeys: 12 days.
Not authorised for use in birds producing eggs for human consumption.

5 PHARMACOLOGICAL or IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterial for systemic use, tetracyclines.
ATCvet-code: QJ01AA02

5.1 Pharmacodynamic properties

Doxycycline is a semisynthetic tetracycline derivative. It acts by inhibiting protein synthesis at the ribosomal level, predominantly by binding to the 30S ribosomal subunits of bacteria. Doxycycline is a broad-spectrum antibiotic. It exhibits a wide range of activity against Gram-positive and Gram-negative, aerobic and anaerobic pathogens, especially against *Mycoplasma gallisepticum* associated with clinical respiratory infections in chickens and turkeys. The MIC_{90} of doxycycline against *M. gallisepticum* strains isolated in France, Germany and Hungary (2003-2009) was reported 0.5 µg/ml.
The resistance rate of *M. gallisepticum* isolates against doxycycline is low (0-6%).
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 transposones). 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 microorganisms with acquired resistance to tetracyclines.

According to the CLSI regulation, organisms other than streptococci with MIC values ≤ 4 µg/ml are considered sensitive, at 8 µg/ml intermediate and with MIC values ≥ 16µg/ml resistant to doxycycline.

5.2 Pharmacokinetic particulars

In general, doxycycline is quite rapidly and extensively absorbed from the gastrointestinal tract, widely distributed in the organism, not metabolised to any significant extent and excreted mostly via the faeces.
Pharmacokinetics of doxycycline after single oral administration to chickens and turkeys is characterised by a quite rapid and substantial absorption from the gastrointestinal tract providing peak plasma concentrations between 0.4 and 3.3 hours in chickens and 1.5 to 7.5 hours in turkeys depending on age and the presence of food. The drug is widely distributed in the organism with V_d values close to or greater than 1, and exhibits shorter elimination half-life in chickens (4.8 to 9.4 hours) than in turkeys (7.9 to 10.8 hours). The protein binding ratio at therapeutic plasma concentrations is in the range of 70-85%. The bioavailability in chickens and turkeys may vary between 41 and 73%, and 25 and 64%, respectively also depending on the age and feeding. The presence of food in the gastrointestinal tract determines a lower bioavailability compared to that obtained in the fasted state.
After continuous in-water administration of the product at dosages of 20 mg doxycycline/kg (chickens) and 25 mg doxycycline/kg (turkeys) for 5 days the average plasma concentrations over the whole treatment period were reported 1.86±0.71 µg/ml in chickens and 2.24±1.02 µg/ml in turkeys. In both avian species the PK/PD analysis of *f*AUC/MIC_{90} data resulted in >24 h values that meet the requirements for tetracyclines.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid, anhydrous
Lactose monohydrate

6.2 Major 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:
- securitainer: 3 years;
- bucket: 2 years.
Shelf life after first opening of the immediate packaging: 3 months.
Shelf life after reconstitution in drinking water: 24 hours.

6.4 Special precautions for storage

Store below 25°C.
Store in tightly closed, original container, in order to protect from light.
Medicated drinking water should be protected from light.

6.5 Nature and composition of immediate packaging

- Securitainer: white polypropylene container, covered with a low-density polyethylene cap.
The securitainer contains 1 kg of product.
- Bucket: white polypropylene container provided with a polypropylene cap.
The bucket contains 1, 2.5 or 5 kg of product.

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 products should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Dopharma Research B.V.
Zalmweg 24
4941 VX Raamsdonksveer
Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

VPA10791/007/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 May 2015
Date of last renewal: 28 May 2020

10 DATE OF REVISION OF THE TEXT

June 2020