[VERSION 8.2, 01/2021]

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ORNICURE 150 mg/g, powder for use in drinking water for racing pigeons and ornamental birds (all CMS except FR)
ORNICURE, powder for use in drinking water for racing pigeons and ornamental birds (FR)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Per 1 gram

Active substance:
Doxycycline hyclate 150.0 mg, equivalent to 130.0 mg of doxycycline

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

3. PHARMACEUTICAL FORM

Powder for use in drinking water.
A fine, light yellow to yellow powder.

4. CLINICAL PARTICULARS

4.1 Target species

Pigeons (racing pigeons) and ornamental birds, particularly Psittaciformes (e.g. African grey parrots, Goffin's cockatoos, cockatiels)

4.2 Indications for use, specifying the target species

Treatment of infections caused by micro-organisms:

- Racing pigeons: treatment of infections caused by *Chlamydophila psittaci, Pasteurella multocida, Mycoplasma spp.*
- Ornamental birds: treatment of infections caused by *Chlamydophila psittaci*

4.3 Contraindications

Do not use in cases of hypersensitivity to the active substance, to other tetracyclines or to any of the excipients.

4.4 Special warnings for each target species

The uptake of medicated drinking water by animals can be altered as a consequence of illness and should be monitored carefully. In case of insufficient uptake of water, it is advised to administer doxycycline directly into the crop or to medicate parenterally.

Medication should be combined with good management practices, e.g. good hygiene and ventilation and, as far as applicable, appropriate stocking density.

Doxycycline (re)absorption may be reduced when birds are given grit. It is therefore recommended to suppress grit and mineral additives during the treatment in pigeons and to limit calcium to a maximum content of 0.7% in pelleted feed in parrots.

Cross-resistance has been shown between doxycycline and others tetracyclines. Use of the product should be carefully considered when susceptibility testing has shown resistance to tetracyclines because its effectiveness may be reduced.

4.5 Special precautions for use

Special precautions for use in animals

Due to the likely variability (time, geographical) in the susceptibility of bacteria to doxycycline, bacteriological sampling and susceptibility testing of micro-organisms originating from diseased animals are strongly recommended.

Use of the product deviating from the instructions given in the SPC/product literature may increase the prevalence of bacteria resistant to doxycycline due to the potential for cross resistance with other tetracyclines and may decrease the effectiveness of the treatment.

Use of the product should take into account official and local antimicrobial policies.
Avoid administration in oxidized drinking equipment.

See section 4.10 for additional warnings.

Toxic concentrations might also be reached in birds housed in hot, outdoor climates where water consumption is increased. Birds undergoing treatment should be monitored for signs of doxycycline toxicosis, including lethargy, inappetance, inactivity, and passing yellow or green urine. Doxycycline toxicosis caused hepatic damage and dysfunction that may result in high plasma AST, lactate dehydrogenase, and bile acids. Doxycycline treatment should be discontinued and general supportive care started if doxycycline toxicosis is suspected.

The quality of the drinking water may influence the bioavailability of the product. See Section 4.9.

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 a possible hypersensitivity to tetracyclines should avoid contact with this veterinary medicinal product.

Take measures to avoid producing dust or inhalation of dust particles when incorporating the product into water. Avoid direct contact with skin and eyes when handling and administering the product.

Wear impermeable gloves (e.g. rubber or latex) and an appropriate dust mask (disposable half-mask respirator conforming to European Standard EN 149 (FFP2) or a non-disposable respirator to European Standard EN 140 with a filter to EN 143) during the preparation and the administration of the solution.

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.

In case of accidental ingestion, seek medical attention.

4.6 Adverse reactions (frequency and seriousness)

As for all tetracyclines, on rare occasions allergic reactions and photosensitivity may occur.
Intestinal flora may be affected if treatment is prolonged (> 10 days), and this may result in digestive disturbance. If suspected adverse reactions occur, treatment should be discontinued.
A slight weight loss may occur.

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

The safety of the veterinary medicinal product has not been established during the reproduction period, i.e., the time period from mating until the end of feeding the progeny. During this time period the use of the product is not recommended.

4.8 Interaction with other medicinal products and other forms of interaction

Concurrent administration of doxycycline with any divalent cations (e.g. Ca, FE, Mg, Al, divalent ions of antacids) should be avoided as this may lead to decreased bioavailability.
Doxycycline may enhance the effect of anticoagulants.
Do not administer together with kaolin, iron preparations and antacids.
Do not use in conjunction with bactericidal antibiotics, such as penicillins, cephalosporins and beta-lactam antibiotics due to antagonism of the mode of action.

4.9 Amounts to be administered and administration route

In drinking water use.

Racing pigeons:

- Treatment of infections due to *Chlamydophyla psittaci*:
  46 mg doxycycline hyclate/day/kg bodyweight for at least 30 days
- Treatment of infections due to other pathogens (*Pasteurella multocida, Mycoplasma spp)*: 20 mg doxycycline hyclate/day/kg bodyweight for 5 days

The medicated drinking water can also be administered directly into the crop.

Ornamental birds, particularly Psittaciformes (e.g. African grey parrots, Goffin's cockatoos, cockatiels):

For the treatment of infections due to *Chlamydophyla psittaci*, the drinking water should be medicated in:

African grey parrots:
at a dose of 800 mg doxycycline hyclate/day/L drinking water ad libitum for 42 days or 54 mg doxycycline hyclate/day/kg bodyweight;

Goffin's cockatoos:
at a dose of 400 mg doxycycline hyclate/day/L drinking water ad libitum for 42 days or 24 mg doxycycline hyclate/day/kg bodyweight;

Cockatiels:
at a dose of 400 mg doxycycline hyclate/day/L drinking water ad libitum (or 40 mg doxycycline hyclate/day/kg bodyweight via feeding tube into the crop) for 30 days.

Owing to physiological and pharmacokinetic differences between the wide range of species for which this product is indicated, the dose rates above are for guidance only. Depending upon the species of animal and the infection to be treated, alternative doses may be appropriate using an evidence-based approach. However, any change in dosing regimen should be based on a benefit:risk assessment by the responsible veterinarian, as tolerance at higher doses has not been investigated.

The exact daily amount of the product can be calculated using the following formula as guidance:

$$\frac{\text{... mg product/kg bodyweight/day*} \times \text{mean bodyweight (kg) of birds to be treated}}{\text{Mean daily water uptake (L) per bird}} = \text{... mg product per L drinking water}$$

* 10 mg doxycycline hyclate/kg bodyweight is equivalent to 67 mg product/kg bodyweight.

To ensure a correct dosage, the body weight should be determined as accurately as possible.

The uptake of medicated drinking water depends on the clinical condition of the birds. To obtain the correct dosage the concentration in the drinking water may have to be adjusted accordingly.

The medicated drinking water is a clear, colourless to yellow solution.

The maximal solubility of the product in soft/hard water at 20°C is around 390 g/L and in soft/hard water at 5°C around 190 g/L.
Warning: The solubility of the product depends on the pH-value; in hard alkaline water the product can precipitate. Water with a hardness of > 19.2°d and a pH-value of > 8.1 is not suitable for dissolving this product.

The use of suitably calibrated weighing equipment is recommended if parts of the 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.

No other source of drinking water should be available during the medication period. Racing pigeons should be kept in the pigeon loft during treatment.
The water supply system should be cleaned appropriately after the end of the medication period to avoid intake of sub-therapeutic amounts of the active substance.

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

Gastrointestinal effects. Ornamental birds and racing pigeons can regurgitate after administration of high dosages.

In Goffin's cockatoos at a dose of 30 mg doxycycline hyclate/kg bodyweight/day for 42 consecutive days, changes in plasma biochemical analyses suggest mild hepatic damage which disappears 7 days after the end of the treatment.

4.11 Withdrawal period(s)

Not authorised for use in birds intended for human consumption. Not for use in birds producing or intended to produce eggs for human consumption.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antibacterial for systemic use, tetracyclines.
ATCvet code: QJ01 AA 02.

5.1 Pharmacodynamic properties

Doxycycline is a semi-synthetic tetracycline derivative.
Doxycycline is a broad-spectrum antibiotic, active against a large number of Gram-positive and Gram-negative, aerobe and anaerobe micro-organisms.
In vitro doxycycline is primarily a bacteriostatic drug. It exerts its action by inhibiting the protein synthesis of the bacterial cell. Doxycycline specifically binds on the receptors of the 30S ribosomal subunits, causing the access of aminoacetyl-tRNA to the receptor location of the RNA-ribosomal complex to be disturbed.
Inhibition of bacterial protein synthesis results in disturbance of all functions necessary for the life of bacteria. Especially cell-division and the formation of the cell wall are impaired.

Based on bibliographic references: C*hlamydophyla psittaci* (2020) and *Mycoplasma spp* (2021) demonstrated to be highly susceptible. *Pasteurella multocida* results (2014) demonstrated a great variability from high to low susceptibility, depending on the geographical region where isolates came from.

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 to tetracyclines is common but depends on the mechanism conferring resistance. 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 via efflux pumps. However, resistance mediated by ribosomal protection proteins confers cross-resistance to doxycycline.

5.2 Pharmacokinetic particulars

The following data are based on bibliographic source:
In general, doxycycline is quite rapidly absorbed from the gastrointestinal tract, widely distributed in the organism, not metabolised to any significant extent and excreted mostly via the faeces.

It was shown that doxycycline was well absorbed from the gastrointestinal tract of the pigeons after an oral dosage of 60 mg/kg b.w. A maximum plasma concentration of 8.1 µg/mL was reached 6 hours after administration and a plasma half-life of 11.3 h was estimated.

At a daily oral dosage of 30 mg doxycycline/kg b.w. divided into 2 equal doses over a time period of 14 days, mean peak-values in the plasma of 2.4 µg/mL and mean trough-values in the plasma of 1.8 µg/mL were measured".

A distribution volume of 1.3-1.4 L/kg was identified in pigeons.

In the liver, a high accumulation (values 8-26 µg/g) was noted 2 h after the last administration, and was slightly reduced after 7 h (single values 7 to 17 µg/g).

For the lung, concentrations significantly higher than in plasma were measured (average plasma levels =1.8 µg/mL after 2 h and 1.4 µg/mL after 6h), although the maximal concentration and the variability is substantially less than in the liver (3-7 µg/g after 2 h and 2 to 4 µg/g after 7 h).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid
Sodium dihydrogen citrate
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

Shelf life of the veterinary medicinal product as packaged for sale: 3 years
Shelf life after first opening the 4 g sachet: use immediately. Do not store.
Shelf life after first opening the 200 g bag: 1 month
Shelf life after dilution or reconstitution according to directions: 24 hours

6.4. Special precautions for storage

This veterinary medicinal product does not require any special temperature storage conditions.
Tightly reclose the 200 g bag after opening in order to protect from light.
Following reconstitution, the medicated solutions should be protected from direct sunlight.

6.5 Nature and composition of immediate packaging

Carton box with 8 single-use aluminium foil sachets, containing 4 g powder each. Each sachet contains 600 mg of doxycycline hyclate.

- Box: carton
- Sachets: Paper-PE-Alu-PE

Polypropylene jar with screw cap containing a bag of 200 g powder.

- Jar: PP
- Scew cap: HDPE
- Bag: Paper-PE-Alu-PE

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

Oropharma n.v.
Kapellestraat 70
BE-9800 Deinze
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: *To be completed nationally*

10 DATE OF REVISION OF THE TEXT

To be completed nationally

PROHIBITION OF SALE, SUPPLY AND/OR USE

To be completed nationally