

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Ladoxyn 500 mg/g granules for oral solution for pigs, chickens and turkeys
(in Cyprus, Czech Republic, Denmark, Greece, Hungary, Italy, Portugal and Spain)

Pulmodox 500 mg/g granules for oral solution for pigs, chickens and turkeys
(in Austria, France, Germany, Slovakia and United Kingdom)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One g granules for oral solution contains:

Active substance:

Doxycycline 500.0 mg
(equivalent to Doxycycline hyclate 580.0 mg)

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Granules for oral solution.
Yellow, free-flowing granules.

4. CLINICAL PARTICULARS

4.1 Target species

Pigs (fattening pigs after weaning), chickens (broilers, broiler breeders) and turkeys (broilers, breeders).

4.2 Indications for use, specifying the target species

Pigs: treatment of clinical respiratory infections caused by *Mycoplasma hyopneumoniae* and *Pasteurella multocida* susceptible to doxycycline.

Chickens and turkeys: treatment of clinical respiratory infections associated with *Mycoplasma gallisepticum* susceptible to doxycycline.

4.3 Contraindications

Do not use in case 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

Inappropriate use of the product may increase the prevalence of bacteria resistant to tetracycline due to the potential for cross resistance.

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.

A high resistance rate of *E. 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.

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

Direct contact of the product with the skin, eyes and mucous membranes should be avoided.

People with known hypersensitivity to tetracyclines should avoid contact with the veterinary medicinal product.

Wear protective gloves and goggles when reconstituting or administering the solution.

Wash exposed skin after preparation. In case of accidental projection into the eyes, rinse abundantly with 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 occasions allergic reactions and photosensitivity may occur. If suspected adverse reactions occur, treatment should be discontinued. If you notice any serious effects or other effects not mentioned in this leaflet, please inform your veterinary surgeon.

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.

The safety of the product has not been established in pregnant or lactating sows. The use is not recommended during pregnancy and lactation.

Do not use in birds in lay and within 4 weeks before the onset of the laying period.

4.8 Interaction with other medicinal products and other forms of interaction

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 pigs and chickens

20.0 mg doxycycline per kg of body weight daily (equivalent to 40.0 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 50.0 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 the 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.

The uptake of medicated water is dependant 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 - approximately 100 grams product per litre drinking water - and to dilute this further to therapeutic concentrations, if required. The maximum solubility of the product in water is 72 g/L. Alternatively; the concentrated solution can be used in a proportional water medicator.

It should be ensured that all animals intended to treat 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 and use in oxidized drinking equipment. Solubility of the product is pH dependent and it will precipitate if it is mixed in an alkaline solution.

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

During the target animal tolerance study, no adverse effect was observed even at the fivefold therapeutic dose administered for two times the recommended duration in either target animal species.

If suspected toxic reactions do occur due to extreme overdose, the medication should be discontinued and appropriate symptomatic treatment should be initiated if necessary.

4.11 Withdrawal period(s)

Meat and offal of pigs: 4 days.

Meat and offal of chickens: 5 days.

Meat and offal of turkeys: 12 days.

Not permitted for use in laying birds producing eggs for human consumption.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Anti-infective 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 *Pasteurella multocida* and *Mycoplasma hyopneumoniae* isolated from pig respiratory infections and *Mycoplasma gallisepticum* associated with clinical respiratory infections in chickens and turkeys. The MIC₉₀ values of doxycycline against *Mycoplasma hyopneumoniae* strains isolated in Spain (2001) and in Belgium (2000-2002) were determined as 0.2 and 0.5 µg/ml, respectively. The MIC₉₀ values for *Pasteurella multocida* isolated in France and the United Kingdom (2002-2004), and Germany (2004-2006) were found to be 2.0 µg/mL. The MIC₉₀ 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. hyopneumoniae*, *P. multocida* and *M. gallisepticum* isolates against doxycycline is low (0-6%). Resistance is mostly due to interference with the active transport of the tetracyclines into, and increased efflux from the cells, or ribosomal protection in which protein synthesis becomes resistant to inhibition. Basically there is a complete cross-resistance within the class of tetracyclines. Doxycycline may be effective against certain strains resistant to conventional tetracyclines due to ribosomal protection or efflux pump mechanisms.

According to the CLSI regulation, organisms other than streptococci with MIC values ≤ 4µg/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.

After oral administration to pigs, doxycycline is substantially absorbed from the gastrointestinal tract. The binding rate to plasma proteins is 93%. It is widely distributed in the organisms; at the steady state, the volume of distribution (V_{SS}) is 1.2 L/kg. Doxycycline is not metabolised to any significant extent and it is excreted primarily in faeces, mostly in a microbiologically inactive form. The elimination half-life was reported to be 4-4.2 hours in pigs. The steady-state plasma concentrations of doxycycline after repeated oral administrations of Ladoxyn/Pulmodox 500 mg/g granules for oral solution for pigs at a dose of 20 mg/kg body weight for 5 days ranged from 1.0 and 1.5 µg/ml. Both the lung and nasal mucosa concentrations at steady-

state were higher than the plasma level. The ratio between tissue- and plasma concentration was found to be 1.3 for lung and 3.4 for nasal mucosa. The doxycycline concentrations both in the lung and the nasal mucosa exceeded the MIC₉₀ of the drug against the target respiratory pathogens.

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 Ladoxyn/Pulmodox 500 mg/g granules 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/MIC₉₀ 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 Incompatibilities

Doxycycline may form insoluble complexes with divalent ions, especially iron or calcium, zinc and magnesium.

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: 3 months

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

6.4. Special precautions for storage

Do not store above 25°C.

Store in the original container tightly closed in order to protect from moisture.

6.5 Nature and composition of immediate packaging

100 g polypropylene container with polypropylene lid and inner bag of LDPE.

1 kg round polypropylene container with polypropylene lid and inner bag of LDPE.

1 kg square polypropylene container with polypropylene lid and inner bag of LDPE.

5 kg round polypropylene container with polypropylene lid and inner bag of LDPE.

5 kg square polypropylene container with polypropylene lid and inner bag of LDPE.

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 products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Lavet Pharmaceuticals Ltd.
1161 Budapest
Ottó u. 14.
Hungary

8. MARKETING AUTHORISATION NUMBER

Vm 32823/4002

9. DATE OF FIRST AUTHORISATION

Date: 20 April 2010

10. DATE OF REVISION OF THE TEXT

Date: November 2013