SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Altidox 500 mg/g powder for use in drinking water for pigs, chickens and turkeys

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each g contains:

Active substance:
Doxycycline 433 mg
(equivalent to doxycycline hyclate 500 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

Pigs (post-weaning), chickens (broilers, pullets, breeders) and turkeys (broilers, pullets, 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 cases of known hypersensitivity to tetracyclines or to 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 impaired liver or kidney function.

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
The safety of the product has not been established in piglets before weaning.
Inappropriate use of the product may increase the prevalence of bacteria resistant to tetracyclines 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.
Use of the product should be based on identification and susceptibility testing of the target pathogen(s). If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target bacteria at farm level, or at local/regional level.
Use of the product should be in accordance with official, national and regional 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
- 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.
- 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.
- People with known hypersensitivity to tetracyclines should avoid contact with the veterinary medicinal product. 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 or a non-disposable respirator to European Standard EN140 with a filter to EN143) 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.
- Do not smoke, eat or drink while 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.

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.

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

Pregnancy and lactation:
Laboratory studies in rats and rabbits have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects.
The safety of the product has not been established in pregnant or lactating sows. Use is not recommended during pregnancy or lactation.

Laying birds:
Do not use in birds in lay or 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. 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 has a low affinity for forming complexes with calcium and studies have demonstrated that doxycycline scarcely affects skeleton formation.
Do not administer together with antacids, kaolin or iron preparations.
Do not administer in conjunction with bactericidal antibiotics such as beta-lactames as tetracyclines are bacteriostatic antimicrobials.
Doxycycline increases the action of anticoagulants.

4.9 Amounts to be administered and administration route

In drinking water use.

Dosage:
In pigs and chickens
20 mg doxycycline per kg body weight daily (equivalent to 46 mg product per kg body weight), administered in the drinking water for 5 consecutive days.
In turkeys
25 mg doxycycline per kg body weight daily (equivalent to 58 mg product per kg body weight), administered in the drinking water for 5 consecutive days.
Administration:
Based on the recommended dosage, and the number and weight of the animals to be treated, the exact daily amount of the product to be administered should be calculated according to the following formula:

.... mg product per kg body weight per day	x	mean body weight (kg) of animals to be treated	= .... mg product per litre of drinking water

mean daily water consumption (litre per animal)

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 condition 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 in such a way that all medication will be consumed within 24 hours. Medicated drinking water should be freshly prepared every 24 hours. It is recommended to prepare a concentrated pre-solution and to dilute this further to therapeutic concentrations, if required. Alternatively; the concentrated solution can be used in a proportional water medicator. The maximum solubility of the product in water is at least 100 g/L.
It should be ensured that all animals intended to be treated 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 or used in oxidised drinking equipment. Solubility of the product is pH-dependent and it may precipitate if it is mixed in hard alkaline drinking water.

4.10 Overdose (symptoms, emergency procedures, antidotes)

During the target animal tolerance study, no adverse effects were observed in any of the target animal species, even at the fivefold therapeutic dose administered for two times the recommended duration.
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 periods

Meat and offal:
Pigs: 4 days.
Chickens: 5 days.
Turkeys: 12 days.
Not authorised for use in birds producing eggs for human consumption.

5. PHARMACOLOGICAL 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 *Pasteurella multocida* and *Mycoplasma hyopneumoniae* isolated from pig

respiratory infections and *Mycoplasma gallisepticum* associated with clinical respiratory infections in chickens and turkeys.
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 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 micro-organisms with acquired resistance to tetracyclines via efflux pumps. However, resistance mediated by ribosomal protection proteins confer cross-resistance 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 primarily in faeces, mostly in a microbiologically inactive form.
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. 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 the veterinary medicinal product 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 MIC_{90} 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 a 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 veterinary medicinal product at doses 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 as 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 $fAUC/MIC_{90}$ data resulted in > 24 h values that meet the requirements for tetracyclines.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric 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: 3 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.
This veterinary medicinal product does not require any special temperature storage conditions.

6.5 Nature and composition of immediate packaging

Bag with an outer layer of polyethylene terephthalate, middle layers of aluminium and polyamide and an inner layer of low density polyethylene (PET/ALU/PA/LDPE).

Pack sizes:
Bag of 1 kg
Bag of 2 kg
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

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

8. MARKETING AUTHORISATION NUMBER

Vm 16849/4056

9. DATE OF FIRST AUTHORISATION

21 October 2016

10. DATE OF REVISION OF THE TEXT

August 2021

Approved 11 August 2021