1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each g contains:

Active substances:

Doxycycline 500 mg
(equivalent to 577 mg of doxycycline hyclate)

Excipients:

Qualitative composition of excipients and other constituents
Citric acid

Yellow powder.

3. CLINICAL INFORMATION

3.1 Target species

Chicken (broiler), pig (for fattening).

3.2 Indications for use for each target species

Chicken (broiler): treatment and methaphylaxis of Chronic Respiratory Disease (CRD) caused by *Mycoplasma gallisepticum* susceptible to doxycycline.

Pig (for fattening): treatment and metaphylaxis of clinical respiratory infection caused by strains of *Pasteurella multocida* susceptible to doxycycline.

The presence of the disease in the group/flock must be established before the veterinary medicinal product is used.

3.3 Contraindications

Do not use in cases of hypersensitivity to the active substance, to other tetracyclines or to any of the excipients.
Do not use in animals with hepatic disorders.
Do not use in animals with renal disorders.

3.4 Special warnings

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.

3.5 Special precautions for use

Special precautions for safe use in the target species:

Use of the veterinary medicinal 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 pathogens at farm level, or at local/regional level.

Use of the veterinary medicinal product should be in accordance with official, national and regional antimicrobial policies.

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.

Avoid administration in oxidised drinking equipment

Inappropriate use of the veterinary medicinal product may increase the prevalence of bacteria resistant to doxycyclin and may decrease the effectiveness of treatment with other tetracyclines due to the potential for cross-resistance.

Do not use at concentrations lower than 0.23 g of powder/l in drinking water with pH higher or equal to 7.5 to avoid precipitation.

Do not add acid to the medicated drinking water.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:

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 veterinary medicinal product and inhalation of dust particles should be avoided.

Take measures to avoid producing dust when incorporating the veterinary medicinal product into water.

Avoid direct contact with skin and eyes when handling the veterinary medicinal product to prevent sensitisation and contact dermatitis.

Personal protective equipment consisting of impermeable gloves (e.g. rubber or latex) and an appropriate dust mask (either a disposable half-mask respirator conforming to European Standard EN149 or a non-disposable respirator to European Standard EN 140 with a filter to EN 143) should be worn when handling the veterinary medicinal product.

In case of accidental eye contact or spillage onto skin, rinse the affected area with large amounts of clean water and if irritation occurs, seek medical advice immediately and show the package leaflet or the label to the physician.

Wash hands and contaminated skin immediately after handling the veterinary medicinal product.

If you develop symptoms following exposure such as skin rash, you should seek medical advice and show the package leaflet or the label 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 veterinary medicinal product.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Chicken (broiler) and pig (for fattening):

Undetermined frequency (cannot be estimated from the available data)	Allergic reactions* Photosensitivity*

*If suspected adverse reactions occur, treatment should be discontinued.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Pregnancy and lactation:
The use is not recommended during pregnancy or lactation.

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

3.8 Interaction with other medicinal products and other forms of interaction

Do not administer together with bactericidal antibiotics (penicillins, aminoglycosides, etc.).

Absorption of doxycycline can be decreased in the presence of high quantities of calcium, iron, magnesium or aluminium in the diet. Do not administered 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.

3.9 Administration routes and dosage

In drinking water use.

Chicken (broiler): 20 mg of doxycycline (equivalent to 40 mg of the veterinary medicinal product)/ kg body weight/day for 3 - 5 days.

Pig (for fattening): 10 mg of doxycycline (equivalent to 20 mg of the veterinary medicinal product) /kg body weight/day for 5 days.

For the preparation of the medicated water, the body weight of the animals to be treated and their actual daily water intake should be taken into due account. Consumption may vary depending on factors like age, state of health, breed, husbandry system. To ensure a correct dosage, body weight should be determined as accurately as possible.

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

$$\frac{\text{mg veterinary medicinal product/kg body weight/day} \times \text{average body weight (kg) of the animals to be treated}}{} =$$

average daily water intake (l/per animal)	mg veterinary medicinal product per liter of drinking water

The intake of medicated water depends on the clinical condition of the animals. In order to obtain the correct dosage, the concentration of doxycycline may need to be adjusted accordingly. Do not use at concentrations lower than 0.23 g of powder/l in drinking water with pH higher or equal to 7.5 to avoid precipitation.

Sufficient access to the system of water supply should be available for the animals to be treated to ensure adequate water consumption. No other source of drinking water should be available during the medication period.

The use of suitably calibrated measuring equipment is recommended.

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 of veterinary medicinal product per liter drinking water - and to dilute this further to therapeutic concentrations if required. Alternatively, the concentrated solution can be used in a proportional water medicator.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

The administration of 40 mg/kg body weight in pig (for fattening) and 80 mg/kg body weight in chicken (broiler) (in both species corresponding to 4 times the recommended dose), for 5 days did not cause any adverse events.
In case of overdose, the treatment should be suspended and symptomatic treatment established.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

Not applicable.

3.12 Withdrawal periods

Pig (for fattening):
Meat and offal: 6 days.

Chicken (broiler):
Meat and offal: 6 days.
Not for use in birds producing eggs for human consumption.
Do not use within 4 weeks before the start of the laying period.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code :
QJ01AA02

4.2 Pharmacodynamics

Doxycycline is a bacteriostatic antibiotic that acts by interfering with the bacterial protein synthesis of sensitive species.

Doxycycline is a semi-synthetic tetracycline derived from oxytetracycline. It acts on the subunit 30 S of the bacterial ribosome, to which is bound reversibly, blocking the union between aminoacyl-tRNA(transfer RNA) to the mRNA-ribosome complex, preventing the addition of new aminoacids into the growing peptide chain an thus interfering with protein synthesis.
Doxycycline is active against, *Mycoplasma* spp. (chicken (broiler)) and *Pasteurella multocida* (pig (for fattening)).

Sensitivity of doxycycline against *Pasteurella multocida* strains isolated from pigs (for fattening) in 2004 has been determined, by means of agar dilution method. MIC_{90} values found are shown in next table (source of breakpoints: NCCLS 2000).
Concentration range used: 0.065 – 16 µg/ml.

NCCLS 2000	*Pasteurella multocida*
MIC_{90}	0.250
Breakpoints	Sensitive ≤ 4µg/ml

MIC_{90} of microorganisms involved in porcine respiratory complex

There are at least two mechanisms of resistance to tetracyclines:

One mechanism is evidenced by decreased ribosome affinity for the tetracycline-Mg^{2+} complex owing to chromosomal mutations. It is a ribosomal protection mechanism, in which protein synthesis is resistant to inhibition through a cytoplasmic protein (Prescott *et al.,* 2000).

The most important mechanism of acquired resistance to tetracyclines is plasmid mediated, and is evidenced by a decrease in the cellular accumulation of the drug. The basis of this decrease is a reduction of the active transport of tetracyclines into the cell due to alterations of the external cellular membrane and increased efflux (or active pump elimination) by acquisition of new transport systems of cytoplasmic membrane. (Prescott *et al.,* 2000). The alteration in the transport system is produced by inducible proteins codified in plasmids and transposons. Because the action mechanism of all tetracyclines has the same base, when resistance occurs, normally there is cross-resistance and complete within its group.

Resistance to tetracyclines may not only be the result of therapy with tetracyclines, but may also be caused by therapy with other antibiotics leading to selection of multi-resistant strains including tetracyclines. although minimal inhibitory concentrations (MIC) tend to be lower for doxycycline than for older generation tetracyclines, pathogens resistant to one tetracycline are generally also resistant to doxycycline (cross resistance). both long term treatment and treating for an insufficient length of time and/or sub-therapeutic dosages can select for antimicrobial resistance and should be avoided.

4.3 Pharmacokinetics

Doxycycline is bio-available after oral administration. When orally administered, it reaches values greater than 70% in most species.

Feeding can modify the oral bioavailability of doxycycline. In fasting conditions bioavailability is around 10 – 15% greater than when the animal is fed. Doxycycline is well distributed through the body as it is highly lipid soluble. It reaches well irrigated tissues as well as peripheral ones. It accumulates in liver, kidney, bones and intestine; enterohepatic recycling occurs. In lungs it always reaches higher concentrations than in plasma. Therapeutic concentrations have been detected in aqueous humour, myocardium, reproductive tissues, brain and mammary gland. Plasma protein binding is 90 – 92%.
40% of drug is metabolized and largely excreted through faeces (biliary and intestinal route), mainly as microbiologically inactive conjugates.

<u>Chicken (broiler):</u>

After oral administration, doxycycline is quickly absorbed, achieving maximum concentrations (C_{max}) around 1.5 h. Bioavailability is 75%. Absorption is decreased in the presence of feed in the gastrointestinal tract, bioavailability is then around 60% and the time to achieve the maximum concentration peak is largely prolonged (t_{max}) 3.3 h.

Pig (for fattening):
Treatment with the recommended dosage, maximum blood concentration in steady state (C_{max-ss}) was 0.83 µg/ml (SD = 0.29) , minimum blood concentration in steady state ($C_{min–ss}$) was 0.22 (SD = 0.07) and C_{ave-ss}= 0.49 (SD= 0.14).
After oral administration of 10 mg doxycycline /kg bw in pigs the bioavailability was 24.8 ± 4.6%. The elimination half-life ($t_{1/2}$) was 4.6 h; plasma clearance was 0.15 l/h.kg and apparent distribution volume was 0.89 l/kg.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

The solubility of the veterinary medicinal product is pH dependent and will precipitate if mixed in alkaline solution.

Do not store the drinking water in metallic containers.

No information is available on potential interactions or incompatibilities of this veterinary medicinal product administered orally by mixing into drinking water containing biocidal products, feed additives or other substances used in drinking water.

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

Shelf life after first opening the immediate packaging: use immediately.

Shelf life after dissolution according to directions: 24 hours.

5.3 Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

5.4 Nature and composition of immediate packaging

Bag formed from polyethylene/aluminium/polyethylene terephtalate laminate.

Pack sizes:
Bag of 400 g.
Bag of 1 kg.

Not all pack sizes may be marketed.

5.5 Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection system applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Huvepharma NV

7. MARKETING AUTHORISATION NUMBER(S)

VPA10782/007/001

8. DATE OF FIRST AUTHORISATION

15/05/2009

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

11/11/2025

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).