Summary of Product Characteristics

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

One gram contains:
Active substance:
Doxycycline (as doxycycline hyclate) 500 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for use in drinking water.
Yellow powder.

4 CLINICAL PARTICULARS

4.1 Target Species

Chickens (broilers)
Pigs (Fattening pigs)

4.2 Indications for use, specifying the target species

Chickens (broilers): Prevention and treatment of Chronic Respiratory Disease (CRD) caused by *Mycoplasma gallisepticum* susceptible to doxycycline.

Fattening pigs: prevention and treatment of clinical respiratory infection caused by strains of *Pasteurella multocida* susceptible to doxycycline.

Use of the product should be based on susceptibility testing of the bacteria isolated from the animal. If this is not possible, therapy should bebased on local (regional, farm level) epidemiological information about susceptibility of the target bacteria.

The presence of the clinical disease in the herd should be established before preventive treatment is started.

4.3 Contraindications

Do not use in cases of hypersensitivity to the active substance, to other tetracyclines or to any excipient. Do not use in animals with hepatic disorders.
Do not use in animals with renal disorders See section 4.7.

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 animalson farm are highly recommended. If this is not possible, therapy should be based on local (regional and farm level) epidemiological information about susceptibility of the target bacteria as well as by taking into account official national 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 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 for 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 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) 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.

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.

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.

4.6 Adverse reactions (frequency and seriousness)

Allergic reactions.
Photosensitivity reactions.

If suspected adverse reactions occur, treatment should be discontinued. Inform your veterinary surgeon if adverse reactions occur that are not indicated.

4.7 Use during pregnancy, lactation or lay

The product should not be used during pregnancy or lactation.
Do not use within 4 weeks of onset of the laying period.

4.8 Interaction with other medicinal products and other forms of interactions

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.
The solubility of the product is pH dependent and will precipitate if mixed in alkaline solution.Do not store the drinking water in metallic containers.

4.9 Amounts to be administered and administration route

To be administered in drinking water.
Chickens (broilers): 20 mg of doxycycline (equivalent to 40 mg of the veterinary medicinal product) / kg BW / day for 3 - 5 days
Fattening pigs: 10 mg of doxycycline (equivalent to 20 mg of the veterinary medicinal product) / kg b.w / 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. Based on the recommended dose, and the number and weight of the animals to be treated, the exact daily amount of hydroDoxx should be calculated according to the following formula:

$$\frac{\text{..... mg HydroDoxx/ kg bodyweight / day} \times \text{Mean body weight (kg) of the animals to be treated}}{\text{Mean daily water consumption (l) per animal}} = \text{.....mg HydroDoxx/ l of drinking water}$$

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. 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 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. Alternatively, the concentrated solution can be used in a proportional water medicator.

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

The administration of 40 mg/kg BW in pigs and 80 mg/kg in chickens (in both species corresponding to 4 times the recommended dose), for 5 days did not cause any adverse reaction.
In case of overdose the treatment should be suspended and symptomatic treatment established.

4.11 Withdrawal period(s)

Meat and offal
Pigs: 6 days
Chickens: 6 days
Not authorised for use in laying birds producing eggs for human consumption. Do not use within 4 weeks of onset of the laying period.

5 PHARMACOLOGICAL or IMMUNOLOGICAL PROPERTIES

ATC Vet Code: QJ01AA02. Doxycycline hyclate.
Therapeutic group: Antibacterial for systemic use; tetracyclines

5.1 Pharmacodynamic properties

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.* (chickens and *Pasteurella multocida* (fattening pigs).

Sensitivity of Doxycycline against *Pasteurella multocida* strains isolated from fattening pigs 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 microgram/ml.

NCCLS 2000	Pasteurella multocida
MIC_{90}	0.25 µg/ml
Breakpoints	Sensitive ≤ 4 µg/ml

MIC_{90} of microorganisms involved in porcine respiratory complex

There are at least two mechanism 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 transposones. 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.

5.2 Pharmacokinetic particulars

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.

CHICKENS
After oral administration, doxycycline is quickly absorbed, achieving maximum concentrations (Cmax) around 1.5 hours. 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 significantly prolonged, (T_{max}) 3.3 hours.

FATTENING PIGS
Treatment with the recommended dosage, maximum blood concentration in steady state ($C_{max\text{-}ss}$) was 0.83 microgram/ml (SD = 0.29) , minimum blood concentration in steady state ($C_{min–ss}$) was 0.22 (SD = 0.07) and $C_{ave\text{-}ss}$= 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 hours; plasmatic clearance was 0.15 l/hour/kg and apparent distribution volume was 0.89 l/kg.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid anhydrous

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: 36 months
Shelf-life after dilution or reconstitution according to directions: 24 hours
After first opening the immediate packaging, discard the unused veterinary medicinal product.

6.4 Special precautions for storage

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

6.5 Nature and composition of immediate packaging

Bag of 1 kg or 400 g formed from polyethylene/aluminium/polyethylene terephtalate laminate.
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

Huvepharma NV
Uitbreidingstraat 80
2600 Antwerpen
Belgium

8 MARKETING AUTHORISATION NUMBER(S)

VPA10782/007/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 15 May 2014

10 DATE OF REVISION OF THE TEXT

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