Summary of Product Characteristics

1 NAME OF THE VETERINARY MEDICINAL PRODUCT

Doxx-Sol 500 mg/g powder for use in drinking water/milk replacer for pre-ruminant calves, pigs and chickens

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains:

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

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

3 PHARMACEUTICAL FORM

Powder for use in drinking water/milk replacer.
Yellowish powder.
Clear solution when dissolved in water.

4 CLINICAL PARTICULARS

4.1 Target Species

Cattle (pre-ruminant calves), pigs, chickens, (broilers, breeders, replacement pullets).

4.2 Indications for use, specifying the target species

Treatment of the following specified infectious diseases of the respiratory tract and the alimentary tract caused by micro-organisms susceptible to doxycycline.

Cattle (Pre-ruminant calves):
- Bronchopneumonia and pleuropneumonia caused by *Pasteurella* spp., *Streptococcus* spp., *Trueperella pyogenes, Histophilus somni* and *Mycoplasma* spp.

Pigs:
- Atrophic rhinitis caused by *Pasteurella multocida* and *Bordetella bronchiseptica*;
- Bronchopneumonia caused by *Pasteurella multocida*, *Streptococcus suis* and *Mycoplasma hyorhinis*;
- Pleuropneumonia caused by *Actinobacillus pleuropneumoniae*.

Chickens (broilers, breeders, replacement pullets):
- Infections of the respiratory tract caused by *Mycoplasma* spp., *Escherichia coli*, *Haemophilus paragallinarum* and *Bordetella avium*;
- Enteritis caused by *Clostridium perfringens* and *Clostridium colinum*.

4.3 Contraindications

Do not use in cases of known hypersensitivity to tetracyclines or to any of the excipients.
Do not use in animals with serious liver or kidney deficiency.
Do not use when tetracycline resistance has been detected in the herd/flock due to the potential for cross resistance
Do not use in ruminating cattle.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals

A high resistance rate of *E. coli*, isolated from chickens, against tetracyclines has been documented. Resistance to tetracyclines has also been reported in pig respiratory pathogens (*A. pleuropneumoniae*, *S. suis*) and calf pathogens (*Pasteurella* spp.) in some EU countries.
Use of the product should be based on identification and susceptibility testing of the target pathogens. If it 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 deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to doxycycline and may decrease the effectiveness of treatment.
Official, national and regional antimicrobial policies should be taken into account when the product is used.
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

Take measures to avoid producing dust when incorporating the product into water.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 known hypersensitivity to tetracyclines should avoid contact with the veterinary medicinal product. 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. Do not smoke, eat or drink while handling 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.

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

The safety of the veterinary medicinal product has not been established in pregnant or lactating sows.
Laboratory studies in rats and rabbits have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects.
Due to depositing of doxycycline in young bone tissue, use of the product should be limited during pregnancy and lactation.
Use only according to the benefit/risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interactions

Do not use in conjunction with bactericidal antibiotics, such as penicillins and cephalosporins.
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. It is advised that the interval between administration of the product and administration of products containing polyvalent cations should be 1-2 hours because the latter limit the absorption of doxycycline.
Doxycycline increases the action of anticoagulants.

4.9 Amounts to be administered and administration route

To be administered orally through the milk-replacer and/or the drinking water.

Cattle (Pre-ruminant calve)s:
for use in milk replacer
10 mg doxycycline hyclate (corresponding to 20 mg of product) /kg body weight / day, divided over 2 administrations, for 3-5 consecutive days.

Pigs:
for use in drinking water
10 mg doxycycline hyclate (corresponding to 20 mg of product) /kg body weight / day, for 3-5 consecutive days.

Chickens (broilers, breeders, replacement pullets):
for use in drinking water
25 mg doxycycline hyclate (corresponding to 50 mg of product) /kg body weight / day, for 3-5 consecutive days.

For the administration through the drinking water, the exact daily amount of product should be calculated, based on the recommended dose, and the number and weight of the animals to be treated, according to the following formula:

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

To ensure a correct dosage body weight should be determined as accurately as possible.
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.
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 - not exceeding 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. The water should be stirred until full dissolution of the product is obtained.
Milk replacer: The veterinary medicinal product must first be dissolved in water before adding the milk powder. The medicated milk replacer should be used immediately and should be freshly prepared after 4 hours at the latest.
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. At the end of treatment period the water supply should be cleaned adequately to avoid the uptake of remaining quantities in sub-therapeutic doses.
The solubility of doxycycline decreases at higher pH. Therefore, the product should not be used in hard alkaline water since precipitation might occur depending on the product concentration. Delayed precipitation might also occur.

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

In calves acute, sometimes fatal myocardial degeneration can occur following single or multiple dosages. Since mostly this is caused by overdosage, it is important to measure the dosage accurately.
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:
Calves: 7 days
Pigs: 8 days
Chickens 5 days
Not for use in birds producing or intended to produce eggs for human consumption.

5 PHARMACOLOGICAL or IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterial for systemic use, tetracyclines
ATC vet code: QJ01AA02

5.1 Pharmacodynamic properties

Doxycycline is a broad spectrum antibiotic. It inhibits bacterial protein synthesis intracellularly by binding on the 30-S ribosome subunits. This interferes with binding of aminoacetyl-tRNA to the acceptor site on the mRNA ribosome complex and prevents coupling of amino acids to the elongating peptide chains.

Doxycycline is a broad-spectrum antibiotic, active against a large number of Gram-positive and Gram-negative, aerobic and anaerobic micro-organisms and *Mycoplasmata*.

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 transposones). Cross resistance between tetracyclines has also been described. 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.

5.2 Pharmacokinetic particulars

Doxycycline is quickly and almost completely absorbed from the intestine. The presence of food in the intestine has no effect on the actual absorption of doxycycline. The distribution of doxycycline and penetration of doxycycline throughout most body tissues is good.
Following absorption, tetracyclines are hardly metabolized. In contrast to the other tetracyclines, doxycycline is mainly excreted via the faeces.

Calves
After a dosage of 10 mg/kg body weight /day during 5 days, an elimination halftime varying between 15 and 28 hours was found. The doxycycline plasma level reached an average of 2.2 to 2.5 µg/ml.

Pigs
In pigs, no accumulation of doxycycline in plasma was found after treatment via the drinking water. Mean plasma values of 0.44 ± 0.12 µg/ml after 3 days of medication with an average dose of 10 mg/kg body weight were found.

Chickens
Steady state plasma concentrations of 2.05 ± 0.47 µg/ml were reached within 6 hours after start of the medication and varied between 1.28 and 2.18 µg/ml with a dosage of 25 mg/kg body weight during 5 days.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid, anhydrous
Lactose monohydrate

6.2 Major incompatibilities

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

6.3 Shelf-life

Shelf life of the veterinary medicinal product as packaged for sale:	30 months
Shelf life after first opening of the immediate packaging:	3 months
Shelf life after reconstitution in drinking water:	24 hours
Shelf life after reconstitution in milk replacer:	4 hours

6.4 Special precautions for storage

This veterinary medicinal product does not require any special conditions.

6.5 Nature and composition of immediate packaging

Bags of 1 kg or 5 kg 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 product 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)

VPA10782/017/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 January 2015
Date of last renewal: 29 January 2020

10 DATE OF REVISION OF THE TEXT

February 2020