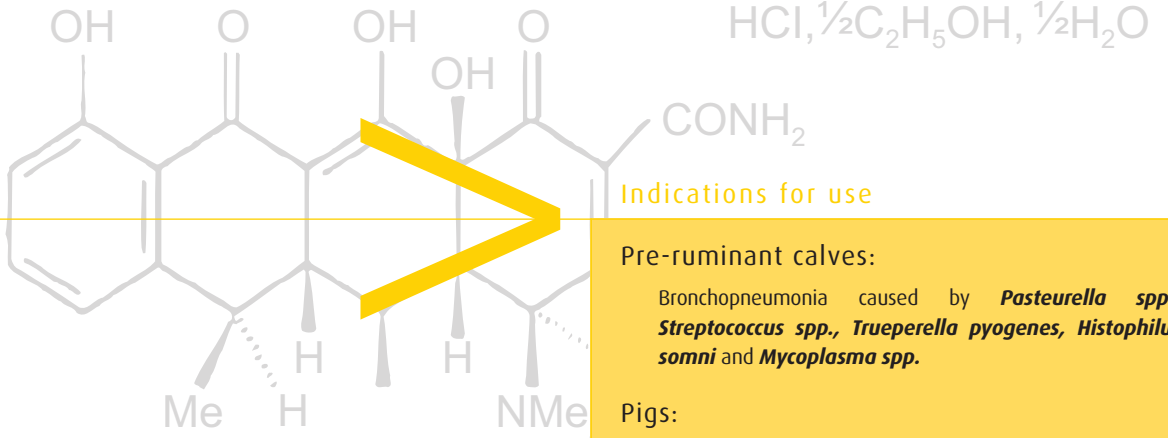
HUVEPHARMA®

Doxx-Sol®

500 MG/G POWDER

FOR USE IN DRINKING WATER AND MILK REPLACER

INTRODUCTION



Origin of the molecule

Doxx-Sol® contains doxycycline hyclate as the active substance, and belongs to the group of tetracycline antibiotics. The tetracyclines are broad spectrum antibiotics that were discovered in the late 1940s. They are so named for their four ("tetra-") hydrocarbon rings ("-cycl-") derivation ("-ine"). There are naturally occurring tetracyclines such as oxytetracycline, chlortetracycline and tetracycline and semisynthetic second generation tetracyclines, such as doxycycline. Elimination times permit a further classification into short-acting (tetracycline, oxytetracycline, chlortetracycline) and long-acting (doxycycline). The tetracyclines are stable as dry powders but not in aqueous solution, particularly at higher pH ranges (7–8.5). Tetracyclines form poorly soluble chelates with bivalent and trivalent cations, particularly calcium, magnesium, aluminum, and iron.

Structure and activity

Doxycycline exhibits the greatest liposolubility and consequently higher bioavailibily and better penetration of bacteria. Doxycycline has a broad-spectrum activity against Gram-negative, Gram-positive, *Chlamydia spp.* and *Mycoplasma spp.* The most common salt form is doxycycline hyclate.

Doxycycline is often used as first line antimicrobial in veterinary medicine.

Product categorization and use

Doxx-Sol® 500 mg/g powder for pigs, chicken (broiler, breeder and replacement pullets) and pre-ruminant calves, is to be used in drinking water and milk replacer. One gram of veterinary product contains 500 mg doxycycline hyclate. Excipients are citric acid and lactose monohydrate.

Indications for use

Pre-ruminant calves:

Bronchopneumonia caused by ***Pasteurella spp., Streptococcus spp., Trueperella pyogenes, Histophilus somni*** and ***Mycoplasma spp.***

Pigs:

Respiratory disease caused by ***Pasteurella multocida, Bordetella bronchiseptica, Streptococcus suis, Mycoplasma hyorhinis*** and ***Actinobacillus pleuropneumoniae.***

Chickens:

Respiratory disease caused by ***Mycoplasma spp., Escherichia coli, Haemophilus paragallinarum*** and ***Bordetella avium.***
Enteritis caused by ***Clostridium perfringens*** and ***colinum.***

Pharmacodynamics

Doxycycline is a broad spectrum antibiotic. It inhibits bacterial protein synthesis intracellularly by binding onto 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.

Time or concentration dependent:

Doxycycline does not have a specific time- or concentration-dependent effect. Both the concentration and the duration of exposure are important.

Spectrum

Doxycycline is a broad spectrum antimicrobial. It is active against a broad range of pathogens, such as:

Mycoplasma spp.
Chlamydiaciae
Pasteurella
Streptococcus
Clostridium
Actinobacillus
Histophilus
Bordetella
Escherichia coli
Clostridium
Haemophilus

Fodor et al. published a study with MIC values for several swine pathogens. Vyt et al. showed some activity of doxycycline against Brachyspirae, however limited and not indicated as treatment. Below you can find the summary of their findings.

Resistance:

Four resistance mechanisms acquired by microorganisms against tetracyclines have been reported, in general:

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.

			MIC if other molecule is added to medium	
Organism	MIC tiamulin	MIC doxycycline	MIC tiamulin (+ doxycycline)	MIC doxycycline (+ tiamulin)
M. hyopneumoniae	0.219	5.169	0.094	0.659
M. hyorhinis	0.219	0.933	0.116	0.094
M. hyosynoviae	0.120	1.101	0.044	0.116
A. pleuropneumoniae	2.297	0.435	1.071	0.088
Past. multocida	2.297	0.125	0.870	0.016
Strep. suis	0.094	0.189	0.044	0.025
B. bronchiseptica	16.0	0.088	5.656	0.017

Table 1. MIC values (µg/ml) of doxycycline of several pathogens. (Fodor et al., 2004)

Molecule	n	Range	MIC50	MIC90
Tiamulin	26	<0.3->16	0,25	8
Doxycycline	26	<0.06-8	1	8
Tiamulin + 16µg/ml doxycycline	12	<0,03->0.03	<0.03	<0.03
Tiamulin + 2µg/ml doxycycline	26	<0.03->16	<0.03	8
Tiamulin + 1µg/ml doxycycline	24	<0.03->16	<0.03	8
Tiamulin + 0.5µg/ml doxycycline	24	<0.03->16	<0.03	8

Table 2. MIC values (µg/ml) of doxycycline of Brachyspira hyodysenteriae.(Vyt P., 2011)

Keypoints:

1. Broad spectrum
2. First line antimicrobial

Pharmacokinetics

Doxycycline differs from tetracycline, oxytetracycline and chlortetracycline as it is more lipophilic, resulting in quick and good absorption 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 throughout most body tissues is good. Accumulation in the synovial fluids and bursae have been described. Following absorption, doxycycline is, in contrast to the other tetracyclines, mainly excreted via the faeces.
Cations differ in their ability to reduce absorption: calcium and zinc do not have a marked effect on absorption, whereas iron decreases absorption markedly.

Non-ruminating calves:

After oral administration of 10 mg doxycycline/kg bodyweight (5 mg/kg BW twice daily) for 5 days:

- Maximum plasma concentration in steady state was 2.3 µg/ml.
- Minimum plasma concentration in steady state was 0.19 µg/ml.
- Elimination half-life was 12.6 hours.

A bioavailibility after oral administration of 70% is mentioned in literature (Meijer et al., 2011).

Pigs:

After oral administration of 11.8 mg doxycycline/kg bodyweight per day for 8 days:

- Maximum plasma concentration in steady state was 1.00 µg/ml.
- Minimum plasma concentration in steady state was 0.73 µg/ml.
- Elimination half-life was 5.92 hours.

A bioavailability after oral administration of 50% is mentioned in literature (Sanders et al., 1996).

Chicken:

After a single oral administration of 20 mg doxcycline/kg bodyweight:

- Maximum plasma concentration in steady state was 5.36 µg/ml.
- Elimination half-life was 13.93 hours.

A bioavailability after oral administration of 60-70% is mentioned in literature (Lacqzay et al., 2001).

Keypoints:

1. Good bioavailability
2. Steady plasma concentrations
3. Long half-life
4. High tissue penetration

Contraindications

Do not use in cases of known hypersensitivity to tetracyclines or to any of the excipients.
Do not administer to animals with severe liver- or kidney insufficiency.

Special warnings for each target species

None.

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 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. Resistance to tetracyclines has also been reported in pig respiratory pathogens *(A. pleuropneumoniae, S. suis)* and calf pathogens *(Pasteurella spp)* in some EU countries.
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.
People with known hypersensitivity to tetracyclines should not handle the 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.

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.

Use during pregnancy, lactation or lay

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.
The safety of the product has not been shown in pregnant or lactating sows.

Interaction with other medicinal products and other forms of interaction

Do not use in conjunction with bactericidal antibiotics, such as penicillins and cephalosporins.
Tetracyclines can chelate cations (e.g. Mg, Mn, Fe and Al) and this may lead to decreased bioavailability.

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.

Solubility

Complete dissolution of a veterinary product is important because:

- Uncompletely dissolved doxycycline can affect bioavailibility
- Of homogeneous dispersion in the drinking water/milk replacer

Doxx-Sol® is soluble in:

- hard water with a high pH
- soft water with a low pH
- milk replacer prepared with hard water
- milk replacer prepared with soft water

Stability

Stability of a dissolved veterinary product is important and depends mainly on:

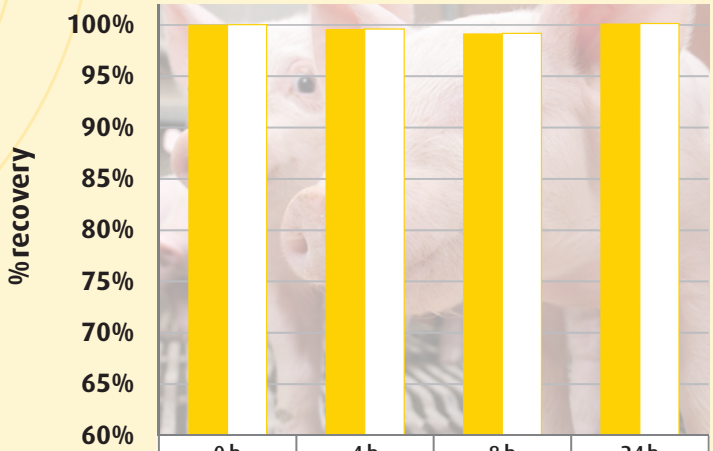
- Formulation
- Water quality

Conclusion

Doxx-Sol® 50% is completely soluble AND stable in drinking water and milk replacer, even at a high pH, and in the presence of divalent cations such as calcium.

	0 hours	2 hours	3 hours	4 hours
■ Soft water/low pH	100%	99%	99%	98%
□ Hard water/high pH	100%	98%	99%	99%

Table 3. Percentage recovery of doxycycline at different time points of Doxx-Sol® dissolved in milk replacer prepared with soft water/low pH and hard water/high pH. (Internal data)



	0 h	4 h	8 h	24 h
■ Soft water/low pH (5,4)	100%	100%	99%	100%
□ Hard water/high pH (8,4)	100%	100%	99%	100%

Table 4. Percentage recovery of doxycycline at different time points of Doxx-Sol® dissolved in drinking) water (170 mg/l) with soft water/low pH and hard water/high pH. (Internal data)

Amounts to be administered and administration route

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

- **Pre-ruminant calves**
  for use in milk replacer
  10 mg doxycycline hyclate/kg body weight/day, corresponding to 20 mg of product per kg body weight, for 3-5 consecutive days, divided over 2 administrations.

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

- **Chickens**
  for use in drinking water
  25 mg doxycycline hyclate/kg body weight/day, corresponding to 50 mg of product per kg body weight, for 3-5 consecutive days.

Practical administration

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:

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

	Doxycycline hyclate per kg bodyweight	Doxx-Sol® per kg bodyweight	Treatment duration
Pre-ruminant calves	10 mg	20 mg	3-5 days, divided over 2 adminis-trations
Pigs	10 mg	20 mg	3-5 days
Chicken	25 mg	50 mg	3-5 days

Withdrawal period

Meat and offal

- Calves: 7 days
- Pigs: 8 days
- Chickens: 5 days

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

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.

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.

* *MA number: UK: Vm 30282/4022, IE: VPA 10782/017/001*
** *Legal Classification: IE Legal category=POM, UK legal category=POM-V*
*** *Use medicines responsibly.*
**** *For further information consult your veterinary surgeon and local country SPC.*

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