**INTRODUCTION**

### 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 *coli*.

### 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, chlorotetracycline and tetracycline and semisynthetic second generation tetracyclines, such as doxycycline. Elimination times permit a further classification into short-acting (tetracycline, oxytetracycline, chlorotetracycline) 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 bioavailability 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.
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 aminoacyl-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.
Chlamydiae
Pasteurella
Streptococcus
Clostridium
Actinobacillus
Histophilus
Bordetella
Escherichia coli
Clostridium
Haemophilus

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 RNA 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.

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC tiamulin</th>
<th>MIC doxycycline</th>
<th>MIC tiamulin (+ doxycycline)</th>
<th>MIC doxycycline (+ tiamulin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. hyopneumoniae</td>
<td>0.219</td>
<td>5.169</td>
<td>0.094</td>
<td>0.659</td>
</tr>
<tr>
<td>M. hyorhinis</td>
<td>0.219</td>
<td>0.933</td>
<td>0.116</td>
<td>0.094</td>
</tr>
<tr>
<td>M. hyosynoviae</td>
<td>0.120</td>
<td>1.101</td>
<td>0.044</td>
<td>0.116</td>
</tr>
<tr>
<td>A. pleuropneumoniae</td>
<td>2.297</td>
<td>0.435</td>
<td>1.071</td>
<td>0.088</td>
</tr>
<tr>
<td>Past. multocida</td>
<td>2.297</td>
<td>0.125</td>
<td>0.870</td>
<td>0.016</td>
</tr>
<tr>
<td>Strep. suis</td>
<td>0.094</td>
<td>0.189</td>
<td>0.044</td>
<td>0.025</td>
</tr>
<tr>
<td>B. bronchiseptica</td>
<td>16.0</td>
<td>0.088</td>
<td>5.656</td>
<td>0.017</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Molecule</th>
<th>n</th>
<th>Range</th>
<th>MIC50</th>
<th>MIC90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiamulin</td>
<td>26</td>
<td>&lt;0.3–&gt;16</td>
<td>0.25</td>
<td>8</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>26</td>
<td>&lt;0.06–&gt;8</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Tiamulin + 16μg/ml doxycycline</td>
<td>12</td>
<td>&lt;0.03–&gt;0.03</td>
<td>&lt;0.03</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Tiamulin + 2μg/ml doxycycline</td>
<td>26</td>
<td>&lt;0.03–&gt;16</td>
<td>&lt;0.03</td>
<td>8</td>
</tr>
<tr>
<td>Tiamulin + 1μg/ml doxycycline</td>
<td>24</td>
<td>&lt;0.03–&gt;16</td>
<td>&lt;0.03</td>
<td>8</td>
</tr>
<tr>
<td>Tiamulin + 0.5μg/ml doxycycline</td>
<td>24</td>
<td>&lt;0.03–&gt;16</td>
<td>&lt;0.03</td>
<td>8</td>
</tr>
</tbody>
</table>

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 chlorotetracycline 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 bioavailability 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 doxycycline/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 (Laqzay et al., 2001).

**Key points:**

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 bacteriostatic 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.
**PRODUCT SPECIFICATIONS**

**Solubility**
Complete dissolution of a veterinary product is important because:
- Uncompletely dissolved doxycycline can affect bioavailability
- 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.

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**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)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Soft water/low pH</th>
<th>Hard water/high pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 h</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>2 h</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>3 h</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>4 h</td>
<td>98%</td>
<td>99%</td>
</tr>
</tbody>
</table>

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**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)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Soft water/low pH (5,4)</th>
<th>Hard water/high pH (8,4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 h</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>4 h</td>
<td>100%</td>
<td>99%</td>
</tr>
<tr>
<td>8 h</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>24 h</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>
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:

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

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.