HUVEPHARMA®

Pharmasin® 100% W/W WSG

TYLOSIN TARTRATE

Indications for use

Pigs

- Treatment and prevention of Porcine Intestinal Adenomatosis (Ileitis) associated with ***Lawsonia intracellularis***.
- Treatment and prevention of enzootic pneumonia caused by ***Mycoplasma hyopneumoniae*** and ***Mycoplasma hyorhinis***.

Origin of the molecule

Pharmasin® 100% Water Soluble Granules (WSG) contain tylosin tartrate W/W. Tylosin is a macrolide antibiotic produced by a strain of *Streptomyces fradiae*. This strain was originally isolated by McGuire *et al*. in 1961 from soil samples, collected from a rice field in Thailand where the antibiotic obtained his name from. Tylosin is registered exclusively for veterinary use and primarily for chronic respiratory diseases like *Mycoplasma spp*. and gastro-intestinal diseases in pigs, poultry and cattle.

Structure and activity

Tylosin is a mixture of four macrolide antibiotics (Tylosin A, B, C and D) produced by a strain of *Streptomyces fradiae*. The main component of the mixture (> 80%) is tylosin A. All four components contribute to the potency of tylosin, which is not less than 900 IU/mg (European Pharmacopoeia 'current edition').

Mode of action

Macrolide antibiotics are bacteriostatic compounds that reversibly bind to the 23S rRNA in the 50S ribosome subunit and inhibit mRNA-directed protein synthesis of susceptible micro-organisms. The tylosin spectrum of activity includes Mycoplasmata, Gram-positive bacteria and some Gram – negative germs.

Product categorization and use

An oral drinking water administration of 1.1 gram of the veterinary medicinal product corresponds to 1 gram of tylosin active. The unique formulation of Pharmasin® 100% WSG is available as granules and are to be used for the preparation of an oral solution for pigs. The granules have a white to creamy white color.

Pharmacokinetic and dynamics

Tylosin is a weak organic base (pKa = 7.73) and it is slightly to moderately bound to plasma proteins (30%). This is creating a high degree of lipid solubility which makes it possible to be widely distributed in body fluids and tissues.

Absorption and Distribution

In pigs, independent of age, Pharmasin® 100% WSG is quickly absorbed from the alimentary tract.

- Peak plasma concentrations are reached within 1 to 2 hours after administration.
- Pharmasin®, was found in all tissues, between 30 minutes and 2 hours after oral administration, except for the brain and spinal cord.
- Compared to plasma levels, tissue concentration levels are clearly higher.
- Tissue/plasma ratios are very high and are reported as volume of distribution V_d of 14.6 g/L.

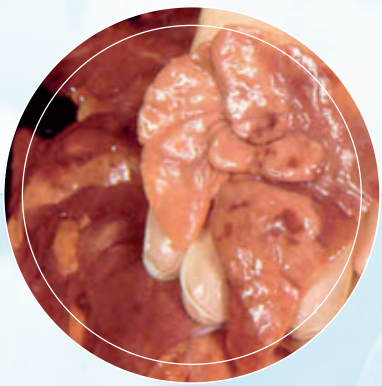
Elimination

Tylosin is extensively metabolized and most of the residues are excreted in faeces predominantly consisting of tylosin A, tylosin factor D and dihydrodesmycosin.

Enzootic pneumonia caused by ***Mycoplasma hyopneumoniae***

Disease

Mycoplasma hyopneumoniae is the primary pathogen of enzootic pneumonia. These infections are highly prevalent in almost all swine producing areas, causing significant economic losses due to an increased medication use and decreased performance of the pigs. *M. hyopneumoniae* is considered one of the primary agents involved in the Porcine Respiratory Disease Complex (PRDC).



Interactions with bacteria

- *M. hyopneumoniae* can infect healthy lung tissue, predisposing pigs to other respiratory infections by different mechanisms such as damaging the epithelium, induction of thick, viscous mucus and modulation of the immune system.
- Combined infections with *M. hyopneumoniae* and *Pasteurella multocida* and/or *M. hyopneumoniae* and *Actinobacillus pleuropneumoniae* result in more severe lesions compared to the single infections.
- Co- or subsequent infections with *P. multocida* and *A. pleuropneumoniae, Bordetella bronchiseptica, Haemophilus parasuis, Arcanobacterium pyogenes, streptococci* or *staphylococci,* are commonly found in field outbreaks of enzootic pneumonia.

Interactions with viruses

- *M. hyopneumoniae* is significantly prolonging and increasing the severity of PRRSV-induced pneumonia.
- A recent experimental study indicated that a *M. hyopneumoniae* infection potentiates the severity of porcine circovirus 2 (PCV2)-associated lung and lymphoid lesions, increases the amount and prolongs the presence of PCV2-antigen, resulting in an increased incidence of post-weaning multi-systemic wasting syndrome in pigs.

Treatment recommendations

To control and treat PRDC including *M. hyopneumoniae* infections in pigs, macrolides (tylosin and tilmicosin) are most frequently used. The reported acquired antimicrobial resistance of *M. hyopneumoniae* does not seem to constitute a major problem for treatment of *M. hyopneumoniae* infections to date.

Pharmasin and Vaccination programs

A Pharmasin® treatment before the infection occurs reduces significantly *M. hyopneumoniae* organisms in the respiratory tract.

- Pharmasin® can be implemented in existing vaccination programs (1 or 2 shot vaccines) as a supplementary prevention tool in herds that are known to carry the disease.
- Next to vaccination, a strategic use of Pharmasin®, mainly in the important and highly sensitive periods*, can be a valuable alternative.

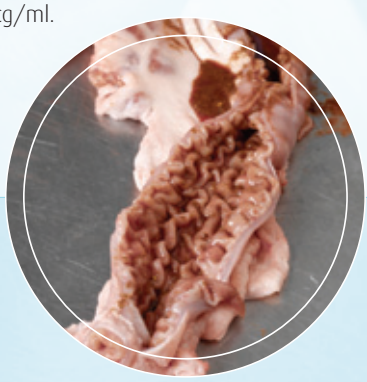
Control Programs

The control of the disease by means of medication can be approached by strategically administering Pharmasin®. A possible treatment scheme in this case would be to start Pharmasin® administration, approximately 1 week prior to the expected time of disease onset. If required, the treatment can be repeated later. A medication regime can limit the severe consequences of the disease and decrease the infection load. This will lead to decreased lung lesions and clinical signs as well as improving the performance parameters.
Antimicrobials or combinations of antimicrobials that are also active against secondary bacteria that often complicate *M. hyopneumoniae* infections are indicated.

Porcine Intestinal Adenomatosis (Ileitis) associated with ***Lawsonia intracellularis***

Disease

Tylosin possesses excellent in vitro and in vivo activity against *Lawsonia intracellularis* (Li), the intracellular causative agent of porcine proliferative enteropathy (PPE, ileitis) and porcine haemorrhagic enteropathy (PHE). Resistance of *Lawsonia intracellularis* to tylosin is rare. The minimum intracellular bactericidal concentration of tylosin against *Lawsonia intracellularis* is <4 mcg/ml.



Treatment recommendations

Pharmasin® is indicated for the treatment and prevention of infections with *Lawsonia intracellularis*, PPE (ileitis) and PHE. Pharmasin® can be administered 4 days prior to the suspected infection and for 7 days after the infection at a dose of 10 mg/kg/BW in the pre-infection period, and 5 mg/kg/BW for 7 days post-infection.
In published studies* where this treatment regime was used, it was demonstrated that none of the pigs in the prevention or treatment programs showed any gross or histopathological signs of *Lawsonia intracellularis* infection. The infected, unmedicated control groups however showed gross lesions in 62.5% of the infected pigs and histopathological lesions in 87.5% of the pigs in the ileum and 37.5% in the caecum. It was concluded that 5 mg/kg/BW tylosin corresponding with 5.5 mg/kg/BW Pharmasin® 100% WSG, was effective for prevention and 10 mg/kg/BW corresponding with 11 mg/kg/BW Pharmasin® 100% WSG for the treatment of PPE (ileitis).

Pharmasin®

Contraindications

Do not use in animals with known hypersensitivity to tylosin or other macrolides and in cases with known resistance to tylosin or cross-resistance to other macrolides (MLS-resistance). Avoid use in animals with hepatic disorders.

Special warnings

Under-dosing and/or treating for an insufficient length of time are considered to promote the development of resistance in bacteria and should be avoided at all times.

Special precautions for use in animals

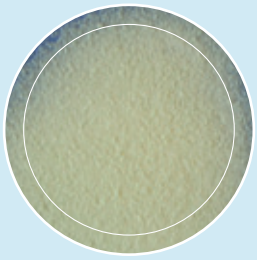
Animals with acute infections may have a reduced water and feed consumption and should be treated with a suitable injectable veterinary medicinal product first. The sensitivity of bacteria to tylosin may have changed over time or geographically. It is sound clinical practice to base treatment on susceptibility testing.

Special precautions for the person administering the veterinary medicinal product to animals

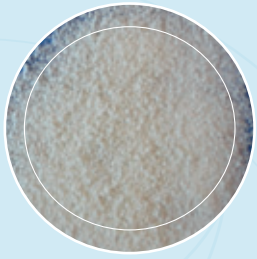
- Because of the possibility of contact dermatitis and irritation of the skin, eyes or respiratory tract, direct contact during administration should be avoided.
- In case of accidental eye contact, wash the eyes thoroughly with water.
- Contact a physician if a skin rash is observed, in the event of oedema of the face, lips or eyes, or if breathing difficulties are encountered.

Product specifications

Pharmasin® water soluble granules have a white to white-creamy color, they are nicely shaped, free flowing, tasteless and dust free. Granules are produced by a fluid bed granulator. With a fast heat transfer technology, the loss of chemical qualities (compound activity) or any alteration of physical characteristics (e.g. color changes) is avoided and the result is flawlessly formed granules.



REF. TYLOSIN

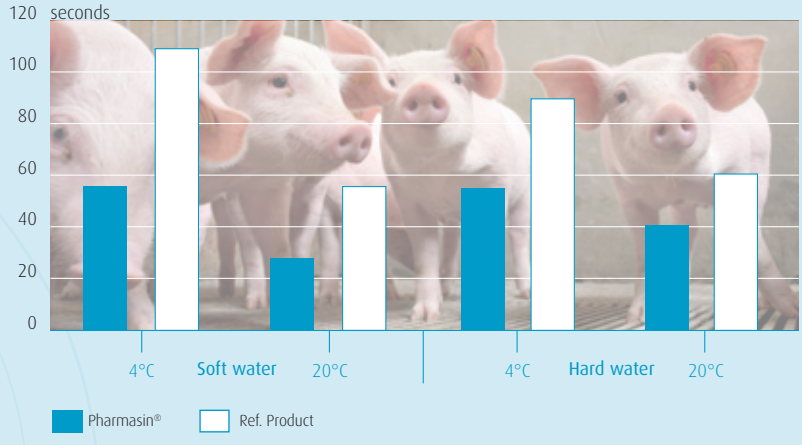


REF. PHARMASIN® WSG

Solubility

Pharmasin® 100% WSG is highly soluble. The solubility was evaluated by comparing the product with a reference sample of tylosin of highest possible concentration. This comparison was made using both soft and hard water of different water temperatures, i.e. 4°C (well) and 20°C (tank) until a clear solution was obtained for both products.
Pharmasin® 100% water soluble granules need less time to fully dissolve, regardless of drinking water qualities. Pharmasin® 100% water soluble granules dissolved in less than 10 minutes which is considered as suitable for use in automatic dosing pumps and water tank applications. In both systems, a concentrated solution can be used, as it will be further diluted in the automatic water supply lines.

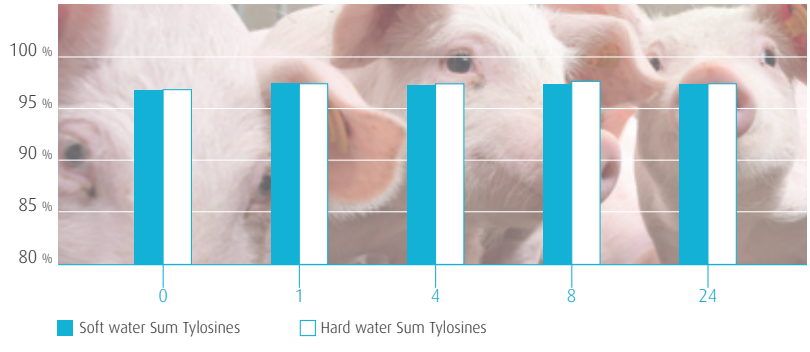
SOLUBILITY PHARMASIN®



Stability

In accordance with the current Committee for medicinal products for veterinary use (CVMP), the stability of medicated drinking water containing Pharmasin® 100% WSG was tested using two types of water. Stability was tested in hard (pH 8-9) and soft water (pH 5-7) and controlled for a period of 24 hours at 25°C. The stability of Pharmasin® 100% WSG was compared to the stability of a reference product representing the sum of Tylosin A, B, C and D.

STABILITY PHARMASIN® DURING 24 HOURS



Dose and administration

An oral drinking water administration of 1.1 gram of the veterinary medicinal product corresponds to 1 gram of tylosin. The dosages are as follows:

Pigs

For the treatment of enzootic pneumonia**:

- **20 mg tylosin per kg BW per day (corresponding to 22 mg of the veterinary medicinal product per kg BW) for 10 days.**

For the treatment of ileitis or PIA**:

- **5-10 mg tylosin per kg BW per day (corresponding to 5.5-11 mg of the veterinary medicinal product per kg BW) for 7 days.**

Practical administration

For the preparation of the medicated water, the body weight of the animals to be treated and their actual daily water consumption should be taken into account.
This consumption depends of age, state of health, breed and husbandry system. In order to provide the required amount of active substance in mg per liter drinking water, the following calculation should be made:

$$\frac{\text{... mg tylosin/kg body weight/day} \times \text{Average body weight (kg) of the animals to be treated}}{\text{Average amount of drinking water/animal (l)}} = \text{... mg tylosin/l of drinking water}$$

No other source of drinking water should be available during the medication period.

Below an overview as example:

	Pharmasin®100% WSG use in gram/animal		
Weight in kg	**5** mg/kg/BW	**10** mg/kg/BW	**20** mg/kg/BW
20	0.11	0.22	0.44
40	0.22	0.44	0.88
60	0.33	0.66	1.32
80	0.44	0.88	1.76

If there is no clear response to treatment within 3 days, the treatment approach should be reconsidered.
After the end of the medication period, the water supply system should be cleaned appropriately to avoid intake of sub-therapeutic amounts of the active substance which might support development of resistance.

Withdrawal period(s)

Meat and offal

- Pigs: 1 day.

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 in medicated water.
- Shelf-life after first opening the immediate packaging: 3 months.

Other species

Pharmasin® 100% WSG is also registered for **Broilers**, **Pullets**, **Turkeys** and **Calves**.

For further information please consult the species related brochure.

Packaging

Pharmasin® is packed in a block bottomed **1.1 kg PET-Alu-PE bag**. The design of the bag makes it possible to close the bag with the included zipper, offering the perfect condition for Pharmasin®.

User warnings:
Because of the possibility of contact dermatitis and irritation of the skin, eyes or respiratory tract, direct contact during administration should be avoided.
Macrolides may induce hypersensitivity reactions (allergy) after injection, inhalation, ingestion or contact with the skin. Cross-hypersensitivity to macrolides may be observed. Allergic reactions to these substances may be particularly hazardous. Therefore, direct contact during administering of the product should be avoided. Hypersensitive persons should avoid all contact with the product. Wear a mask, safety glasses and protective gloves when either reconstituting or administering the solution. After preparation of medicated water, wash exposed skin with soap and water. In case of accidental eye contact, wash the eyes thoroughly with water. Contact a physician immediately if a skin rash is observed, in the event of oedema of the face, lips or eyes, or if breathing difficulties are encountered.

* Used references can be obtained on demand.
** Pharmasin® 100% WSG brochure is following the authorized EU SPC.
*** Indications listed above are not necessarily authorized in all countries.
For further information, consult your veterinarian surgeon and local country SPC.
Please consult the local label for exact indications and posology.
**** Use medicines responsible- Legal Category: UK POM-V/IE POM.

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