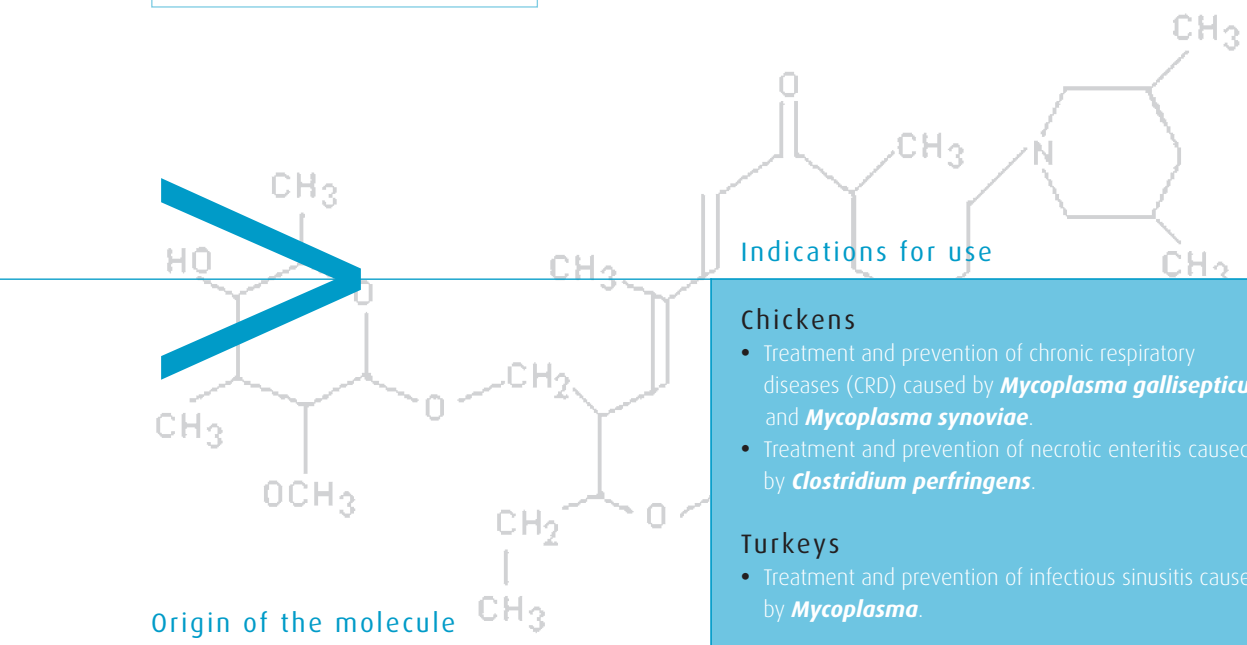
HUVEPHARMA®

Pharmasin® 100% W/W WSG

TYLOSIN TARTRATE



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.

Indications for use

Chickens

- Treatment and prevention of chronic respiratory diseases (CRD) caused by ***Mycoplasma gallisepticum*** and ***Mycoplasma synoviae***.
- Treatment and prevention of necrotic enteritis caused by ***Clostridium perfringens***.

Turkeys

- Treatment and prevention of infectious sinusitis caused by ***Mycoplasma***.

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 poultry. 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

In poultry, Pharmasin® 100% WSG is quickly absorbed from the alimentary tract. Tylosin reaches maximum blood levels between 1 and 3 hours after oral administration.

Elimination

Pharmasin® 100% W/W is extensively metabolized, and most of the residues are excreted in faeces pre-dominantly consisting of tylosin A, tylosin factor D and dihydrodesmycosin.

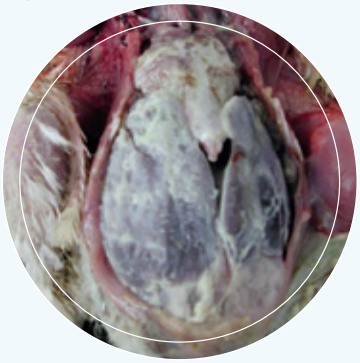
Chronic respiratory disease caused by ***Mycoplasma gallisepticum*** and ***Mycoplasma synoviae*** in chickens and turkeys

Disease

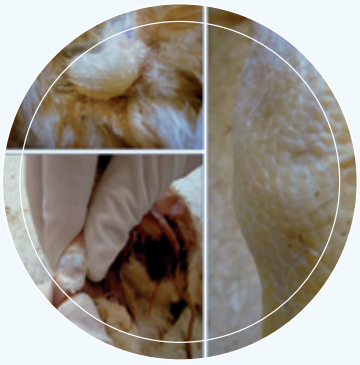
Mycoplasma infections are still considered as a major worldwide disease in modern poultry industry and are mainly caused by:

- *Mycoplasma gallisepticum*
- *Mycoplasma synoviae*

Mycoplasma bacteria are transmitted vertically and establish long life infections in their host. Severity of clinical signs is strongly influenced by concurrent viral or bacterial infections and environmental factors. *Mycoplasma gallisepticum* infected chicken flocks will suffer from respiratory symptoms, decreased performance and increased condemnations at processing.



In recent years, *Mycoplasma synoviae* is believed to be of growing importance as a cause of economical losses due to synovitis and respiratory disease.
In turkeys, *Mycoplasma gallisepticu*m causes infectious sinusitis inducing sinusitis, pneumonia and airsacculitis. Clinical sings consist of nasal and ocular discharge; typically the paranasal sinuses will be swollen.
Furthermore, animals may suffer from tracheal rales, coughing, labored breathing and loss of condition. In breeder flocks, Mycoplasma infections may cause a drop in egg production or reduced production efficiency.



Interactions with other pathogens

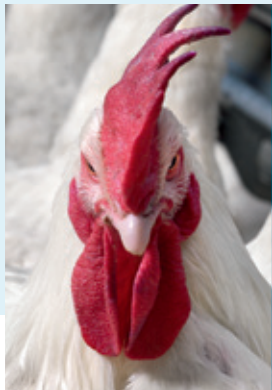
- *Mycoplasma gallisepticum* infections in poultry predispose the chickens or turkeys to other respiratory infections by different mechanisms.
- Combined infections in chickens with other bacteria such as *Escherichia coli* or combined infections with *Infectious Bronchitis* virus or Newcastle Disease result in more severe lesions compared to the single infections.
- In turkeys, combined infections of *Mycoplasma gallisepticum* and other bacteria such as *Escherichia coli, Ornithobacterium rhinotracheale* or viruses like Avian Pneumoviruses have been described.

Mycoplasma control

In many countries, control of the disease is based upon eradication of infected breeding flocks. In layers and in areas were *Mycoplasma gallisepticum* has not been eradicated in breeders, antibiotic therapy and vaccination are used to control the disease. In general, layer flocks are known to be an important reservoir of Mycoplasma infections. Many breeding flocks cannot maintain a Mycoplasma free status during life. Recently, also the role of wild birds as a possible source of infection for commercial poultry has been emphasized.

Vaccination generally results in protection against vertical transmission, reduction of clinical signs and drops in egg production. However, vaccination is insufficient to prevent completely a horizontal spreading of *Mycoplasma gallisepticum*. Therefore, vaccinated birds can still be a threat and keep spreading the disease.

Medication is a very important tool to control the clinical signs and the transmission of Mycoplasma infections. To prevent antibiotic resistance in other bacteria, it is preferred to use Mycoplasma selective antibiotics like Pharmasin® 100% WSG over broad-spectrum antibiotics. Pharmasin® should be applied in appropriate schemes that maximize the (clinical) effect and minimize the risk for resistance development.



Necrotic enteritis caused by ***Clostridium perfringens***

Disease

Clostridium perfringens, a gram positive, anaerobic spore-forming bacillus is the main causative agent of necrotic enteritis in birds. This disease is characterized by reduced growth performance, decreased feed efficiency and depression in its chronic form and by anorexia, high morbidity and significant mortality in the acute form.
Clostridium perfringens is ubiquitous in the environment, being isolated out of soil, dust, litter, faeces, feed and water and is a normal inhabitant of the intestinal tract of many animals and humans. Predisposing factors for necrotic enteritis outbreaks in commercial poultry flocks appear to be high protein, high fiber or wheat diets and coccidiosis infections. In Europe, the ban of growth promoters in feed has led to more outbreaks of necrotic enteritis.

Treatment recommendations

Pharmasin® is indicated for the treatment and control of necrotic enteritis in poultry. Trials with tylosin using a chick model for inducing necrotic enteritis, have shown that tylosin reduces the general percentage of mucolytic bacteria and in particular the concentration of *Clostridium perfringens* in the small intestine.
These responses were correlated in a temporal fashion with a reduction in the occurrence of necrotic enteritis lesions and an improvement in barrier function. Tylosin appears to control necrotic enteritis through the modulation of *Clostridium perfringens* colonization and the mucolytic activity of the intestinal microbiota.

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

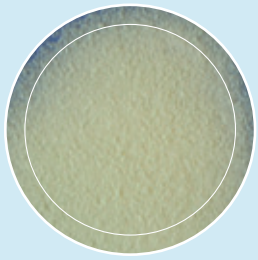
Animals with acute infections may have a reduced water and feed consumption and should be treated with a suitable injectable veterinary medicinal product first. The sensitivity of bacteria to tylosin may have changed over time or geographically. It is sound clinical practice to base treatment on susceptibility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

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

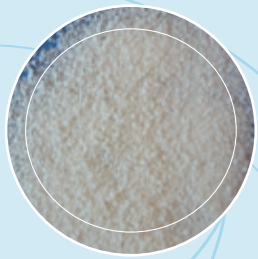
- Because of the possibility of contact dermatitis and irritation of the skin, eyes or respiratory tract, direct contact during administration should be avoided.
- In case of accidental eye contact, wash the eyes thoroughly with water.
- Contact a physician if a skin rash is observed, in the event of 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) is avoided and the result is flawlessly formed granules.



REF. TYLOSIN

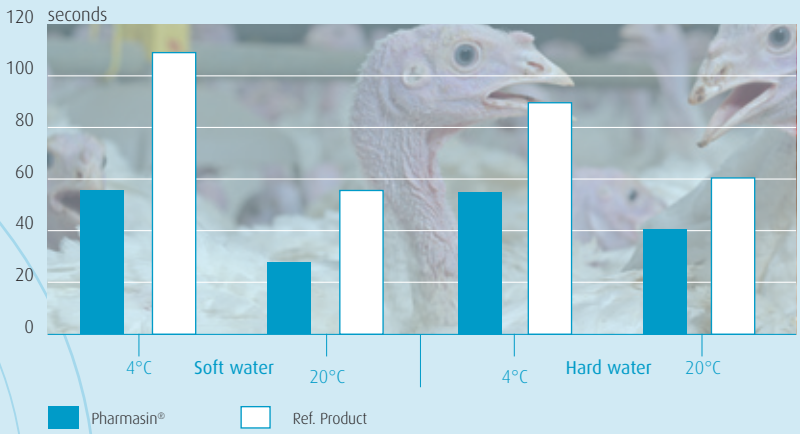


REF. PHARMASIN® WSG

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.

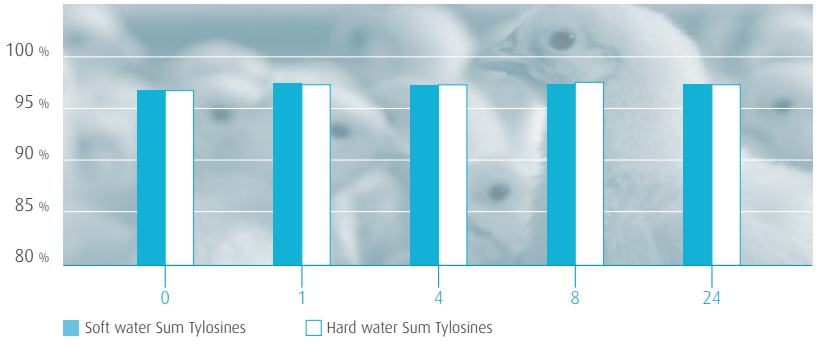
SOLUBILITY PHARMASIN®



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

To be administered and administration route:
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:

Chickens (Broilers, pullets)

For the treatment of chronic respiratory disease:

- **75-100 mg tylosin per kg BW per day (corresponding to 82.5-110 mg of the veterinary medicinal product per kg BW) for 3-5 days**.

For the treatment of necrotic enteritis:

- **20 mg tylosin per kg BW per day (corresponding to 22 mg of the veterinary medicinal product) for 3 days.**

Turkeys

- **75-100 mg tylosin per kg BW per day (corresponding to 82.5-110 mg of the veterinary medicinal product per kg BW) for 3-5 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. 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	**20** mg/kg/BW	**75** mg/kg/BW	**100** mg/kg/BW
1000	22	82.5	110

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

- Chickens (meat and offal): 1 day
- Chickens (eggs): 0 days
- Turkeys (meat and offal): 2 days
- Turkeys (eggs): 0 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% W/W is also registered for **Pigs** 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 requested on demand.
* Pharmasin®100% W/W brochure is following the authorized EU SPC.
** Indications listed above are not necessarily authorized in all countries. Please consult the local label for exact indications and posology.

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