HUVEPHARMA®

Pharmasin®

250 MG/G PREMIX

TYLOSIN PHOSPHATE

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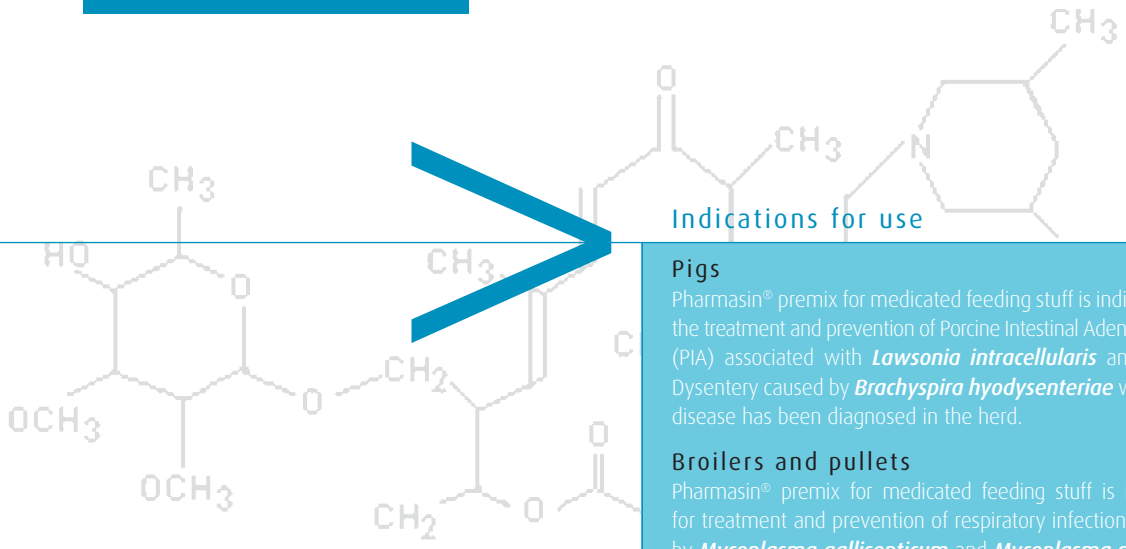
AgriHealth
Evidence based vet medicines

INTRODUCTION



Indications for use

Pigs

Pharmasin® premix for medicated feeding stuff is indicated for the treatment and prevention of Porcine Intestinal Adenomatosis (PIA) associated with ***Lawsonia intracellularis*** and Swine Dysentery caused by ***Brachyspira hyodysenteriae*** when the disease has been diagnosed in the herd.

Broilers and pullets

Pharmasin® premix for medicated feeding stuff is indicated for treatment and prevention of respiratory infections caused by ***Mycoplasma gallisepticum*** and ***Mycoplasma synoviae*** and necrotic enteritis caused by ***Clostridium perfringens*** when the disease has been diagnosed in the flock.

Origin of the molecule

Pharmasin® 100 & 250 mg/g premix for medicated feeding stuff contains tylosin (as tylosin phosphate). 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 its name from. It is registered exclusively for veterinary use.

Structure and activity

Tylosin is a mixture of four macrolide antibiotics (tylosin A, B, C and D). The main component of the mixture (> 80%) is tylosin A, however all four components contribute to the potency of tylosin.

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 and some Gram – negative bacteria.

Product categorization and use

Pharmasin® premix for medicated feeding stuff is available in a 100 mg/g and a 250 mg/g concentration. One kilogram of the veterinary medicinal product respectively contains 100 gram and 250 gram of tylosin. A water soluble formulation for medicated drinking water use in pigs and poultry and granules for individual treatment in pigs are also available.

Pharmacokinetic and dynamics

Tylosin is a weak organic base (pKa = 7.1) and it forms readily water soluble salts with the mineral and organic acids (tartrate, phosphate, lactate, etc.). 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 most species peak plasma concentrations have been attained 1 to 2 hours after administration of tylosin. Compared to plasma levels clearly higher tissue concentrations have been observed.

It has also been established that regardless of the way of administration, tylosin resorbed by the digestive system canal is brought to the blood flow and is slightly to moderately bound to plasma proteins. It penetrates in all organs, tissues and fluids to different rates due to its high lipid solubility. Tylosin is found to be highly absorbed and well distributed in different animal species, especially in pigs where the volume of distribution (Vd) reaches 14.6 l/kg (Prats *et al.* 2002). This explains the observation made by Vicca *et al.* (2005), who found high concentrations of tylosin in lung macrophages which reduced the clinical symptoms and lung lesions related to *M. hyopneumoniae* infections after 3 weeks of treatment with 100 ppm of tylosin.

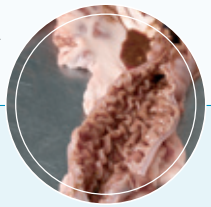
Elimination

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

Porcine Intestinal Adenomatosis (Ileitis) associated with ***Lawsonia Intracellularis*** in pigs

Disease

Tylosin possesses excellent activity against *Lawsonia Intracellularis* (LI), the intracellular causative agent of porcine proliferative enteropathy (PPE), porcine intestinal adenomatosis (PIA or ileitis) and porcine haemorrhagic enteropathy (PHE).



Treatment recommendations

Pharmasin® is indicated for the treatment and prevention of LI related diseases. For the treatment and prevention of PIA it is recommended to add 4-5 mg of tylosin per kg BW to the feed for 3 weeks to be fully effective.

Published recommendations

In publications made by McOrist, the strategic use of medication to control Ileitis infections is described as being inherently part of a control strategy which should also include general hygiene, weaning age/weight, feeding strategy and feed composition but also serological profiling (detailing level of exposure and breaking of the herd). Continuously exposed herds (at all levels: sows, replacement gilts, grower finishers) were found and described as being highly dependent on medication, whereas herds with a lower infection pressure needed a combination of cleaning and disinfection, and medication.

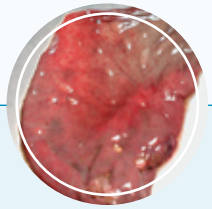
As the disease can recur a few weeks after the end of the treatment, it was stated by different authors that an additional treatment can be given 3 weeks after the end of the first treatment and this upon the advice of the responsible veterinarian. This additional treatment will depend on the infection levels found on the farm and its managerial situation. Therefore, various authors stated that different treatment rounds were beneficial to overcome clinical symptoms related to LI.

(ref. available on request)

Swine dysentery caused by ***Brachyspira hyodysenteriae*** in pigs

Disease

Swine dysentery (SD) is a highly fatal enteric disease characterized by bloody diarrhoea, poor productivity and death.



PICTURES: COURTESY OF P. VYT, MEDIC LAB, AALST, BELGIUM

Treatment recommendations

SD occurs in most major pig producing countries worldwide and represents a major health issue. Economic losses from decreased feed efficiency have been estimated at four times the medication cost. Morbidity can range from 10 to 75% and if sick animals are not treated, the mortality rate can be as high as 50%.

Depending on the infection severity and the effectiveness (resistance), Pharmasin® can be used with a standard dose during 4-5 weeks or at a double dose for 8 days, followed by the standard dose until the end of the period of risk.

Pharmasin®

Respiratory diseases caused by ***Mycoplasma gallisepticum*** and ***Mycoplasma synoviae*** in broilers and pullets

Disease

Mycoplasma infections are considered as being a major worldwide disease in the modern poultry industry. The bacteria causing the infections are transmitted vertically and establish life-long infections in the host. Severity of clinical signs is highly influenced by concurrent viral or bacterial infections and environmental factors. Infected animals are predisposed to combined infections (e.g. *E.coli*, infectious bronchitis, Newcastle disease).

Treatment recommendations

In many countries, the control of the disease is based upon eradication of infected breeding flocks. Alternatively, antibiotic therapy and vaccination are used, particularly in laying flocks known to be an important reservoir of infection. Medication is a crucial tool to control clinical signs and the transmission of Mycoplasma infections. However, the use of selective antibiotics is preferred over broad-spectrum antibiotics to avoid resistance build-up. Therefore, Pharmasin® should be applied in appropriate schemes maximizing the (clinical) effect and minimizing the risk for resistance development. It is advised to treat young animals at a dose of 127 mg tylosin per kg BW the first 5 days of life and it is strongly recommended to repeat the treatment at the age of 3 to 4 weeks.

Necrotic enteritis caused by ***Clostridium perfringens*** in poultry

Disease

Clostridium perfringens (present everywhere in the environment and intestinal tract) is the main causative agent of necrotic enteritis (NE) in birds, resulting in reduced growth performance, decreased feed efficiency, depression, anorexia, severe morbidity and significant mortality. Predisposing factors include 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 NE.

Treatment recommendations

Pharmasin® is recommended for the treatment and control of NE. Tylosin is known to control NE through the modulation of *Clostridium perfringens* colonization and the mucolytic activity of the intestinal microbiota. A successful treatment consists of the administration of 10 to 20 mg tylosin per kg BW for 7 days.

Contraindications

Do not use in animals with known sensitivity to the active substance and/or to any of the excipients. Also, do not use in animals with known hypersensitivity to tylosin and other macrolides or in case cross-resistance to other macrolides (MLS-resistance) is suspected. The product should not be used in animals that were vaccinated with tylosin-sensitive vaccines either at the same time or 1 week prior to administration. Do not use in horses or in animals with hepatic disorders.

Adverse reactions

In pigs, adverse reactions have been observed, including diarrhoea, pruritis, erythema, rectal oedema and prolapse.

Special warnings

Animals with acute infections may have a reduced feed intake and should be treated with a suitable injectable product first.
In farms which have recurring problems with swine dysentery, farm management, livestock husbandry and hygiene should be examined to avoid repeated administration of antimicrobial substances. An eradication procedure should be taken into account.

Special precautions for use in animals

The use of Pharmasin® premix in medicated feeding stuff should be based on susceptibility testing and should take into account official and local antimicrobial policies. The sensitivity of bacteria to tylosin may have changed over time or geographically. If there is no treatment response within 3 days the treatment approach should be reconsidered. As laboratory studies in mice and rats did not produce any evidence of teratogenic, foetotoxic or maternotoxic effects, the use of Pharmasin® premix during pregnancy, lactation or laying should be done in accordance to the benefit/risk assessment by the veterinarian.

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

Tylosin may induce irritation and macrolides may also cause hypersensitivity (allergy) following injection, inhalation, ingestion or contact with skin or eyes. This may lead to cross reactions to other macrolides or vice versa. Direct contact should be avoided by wearing suitable protective clothing (overalls, safety glasses, impervious gloves, mask) at all times as allergic reactions may occasionally be serious. In case of accidental skin contact, wash thoroughly with soap and water. In case of accidental eye contact, flush the eyes with plenty of clean running water. If symptoms were developed following exposure, seek immediate medical advice. Swelling of face, lips and eyes or difficult breathing are more serious symptoms and require urgent medical attention.

PRODUCT SPECIFICATIONS

Product specifications

The granules of Pharmasin® premix for use in medicated feeding stuff are creamy to slightly white colored. They are nicely shaped, free flowing, tasteless and dust free. Produced by a fluid bed granulator and with a fast heat transfer technology, guaranteeing the loss of chemical qualities (compound activity) or any alteration of physical characteristics (e.g. color) is avoided. This production technique results in flawlessly formed granules.

Stability and in-use stability

Pharmasin® premix was tested with regard to mixing uniformity, transport segregation and processing/storage stability in a typical and complete European pig and broiler diet. In addition, proximate analysis, including dry matter content of the diets and quality assessments of the pelleted feed were performed. The tylosin target inclusion rate was examined at the lowest and highest possible levels.

Storage stability tests performed at 25-30°C lead to the conclusion that the product has remained well within the quality specifications after 3 months, which is the suggested validity period of the medicated feed, regardless of type of feed, pellet or mash.

Homogeneity

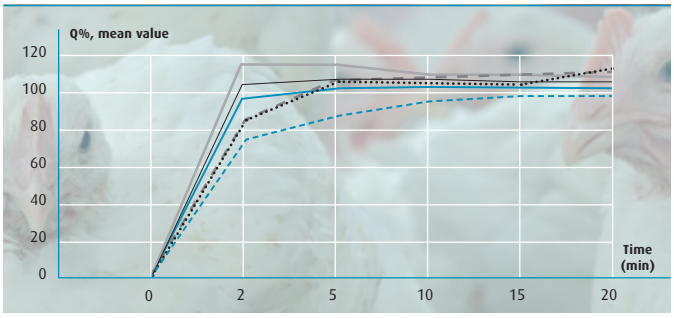
In terms of mixing uniformity, tylosin assay levels in both pig and broiler diets were all around the target level for both inclusion levels. All samples showed standard deviations well below 5%, being the maximum percentage of deviation with regard to the mean, thus confirming the homogeneity. The mixing uniformity could be considered good to excellent.

There were no indications for segregation as a result of transport found in the studies nor was there any proof observed of significant loss of activity of tylosin as a result of conditioning/pelleting.

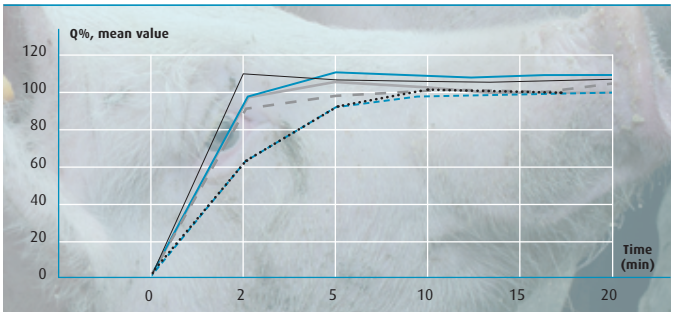
Dissolution

The dissolution profiles of Pharmasin® 100 mg/g & 250 mg/g premix were compared *in vitro* applying the method described in the European Pharmacopeia, item 2.9.3. with two competing tylosin phosphate premix formulations. They were tested in 3 different dissolution media – pH 1.2, pH 4.6 and pH 7.5. All products were well above the dissolution rate of 85% after 15 minutes which is considered enough to guarantee bioavailability.

COMPARATIVE DISSOLUTION TEST OF PHARMASIN® 100 MG/G PREMIX WITH COMPETING FORMULATIONS



COMPARATIVE DISSOLUTION TEST OF PHARMASIN® 250 MG/G PREMIX WITH COMPETING FORMULATIONS



	Concentration	Disease	Recommended dose		Treatment period/duration
			Tylosin/kg BW	Pharmasin PM/kg BW	
Pigs	**250 mg/g**	PIA	4-5 mg	16-20 mg	3 weeks
		Dysentery	4-5 mg	16-20 mg	4-5 weeks
		Dysentery	8-10 mg	32-40 mg	8 days and 4-5 mg until end
Broilers/pullets	**250 mg/g**	Respiratory infection	127 mg	508 mg	first 5 days, repeat at 3-4 weeks of age
		Necrotic Enteritis	10-20 mg	40-80 mg	7 days

Amount(s) to be administered and administration route

Medicated feed must be prepared taking into account the above-mentioned recommended doses for each condition and species.

Practical administration

For the preparation of the medicated feed, the required amount of Pharmasin® premix should be homogenously mixed with a suitable amount of feed so that at least 5 kg of this prepared feed can be added into the blender/mixer in order to obtain a medicated feed with the required concentration. The body weight of the animals to be treated and their actual daily feed consumption should be taken into due account. Mixing should be performed by an (authorized) feeding stuff manufacturer with adequate mixing apparatus. The uptake of medicated feed depends on the clinical condition of the animals. In order to obtain the correct dosage the concentration of tylosin should be adjusted accordingly.

To provide the required amount of active substance in mg per kg mixed feed the following calculation should be made.

$$\frac{\text{... mg Pharmasin® premix per kg BW/day} \times \text{Average BW (kg)}}{\text{Average daily amount of mixed feed intake in kg per animal}} = \text{... mg Pharmasin® premix per kg/ mixed feed}$$

Example:
Assuming PIA treatment in pigs weighing 50 kg, dose is 4 mg/kg BW. The animals have a daily feed consumption of 2 kg: the user would need to add 1 kg of Pharmasin® 100 mg/g premix or 400 g of Pharmasin® 250 mg/g premix for use in medicated feeding stuff per ton of feed.

Withdrawal period(s)

Meat and eggs

- Pigs: Nil
- Broilers and pullets: Nil
- Eggs: Nil

Shelf-life and storage

- Shelf-life of the veterinary medicinal product as packaged for sale: 2 years.
- Shelf-life after incorporation into meal or pelleted feed: 3 months.
- Store the original packaging in a dry place and protect from direct sunlight at temperatures below 30°C. Do not refrigerate or freeze.

Incompatibilities

In the absence of compatibility studies Pharmasin® premix must not be mixed with other veterinary medicinal products. Lincosamides and aminoglycoside antibiotics are known to antagonize the activity of tylosin.

Packaging

Pharmasin® premixes for use in medicated feeding stuff are packed in low-density PE/paper bags of 5 and 20 kg with sutured crimp.

Check with your local Huvepharma representative which pack sizes are available in your region as this may vary.

User warnings:
Tylosin may induce irritation. Macrolides may cause hypersensitivity following injection, inhalation, ingestion or contact with skin or eyes. Direct exposure during preparation of the medicated feed should be avoided, therefore wear overalls, safety glasses, impervious gloves and wear either a disposable half mask respirator or a non-disposable respirator with a filter to EN143. Wash hands after use. In the event of accidental skin contact, wash thoroughly with soap and water. In case of accidental eye contact, flush the eyes with plenty of clean, running water. Do not handle the product if you are allergic to its ingredients. Seek medical advice if you develop symptoms following exposure. Swelling of the face, lips and eyes or difficulty in breathing are more serious symptoms and require urgent medical attention. Any unused product or waste material should be disposed of in accordance with national requirements.

* *Used references can be requested on demand.*
** *Pharmasin® premix for use in medicated feeding stuff is following the authorized EU SPC (available at request).*
*** *Indications listed above are not necessarily authorized in all countries. Please consult the local label for exact indications and posology.*

References:
Vicca, J. (2005) Virulence and antimicrobial susceptibility of *Mycoplasma hyopneumoniae* isolates from pigs, Thesis to obtain the academic degree of Doctor of Veterinary Science (PhD), Faculty of Veterinary Medicine, Ghent University.

HUVEPHARMA®