HUVEPHARMA®

Tilmovet®

MEDICATED FEED PREMIX CONTAINING TILMICOSIN

Indications for use

Pigs

Prevention and treatment of respiratory disease caused by ***Actinobacillus pleuropneumoniae, Mycoplasma hyopneumoniae, Pasteurella multocida*** and other organisms sensitive to tilmicosin.

Origin of the molecule

Tilmovet® Medicated Premix contains tilmicosin. It is a semi-synthetic macrolide antibiotic obtained from tylosin which is affecting bacterial protein synthesis. Macrolides have been used for decades as treatment for a wide range of infectious diseases, but their effect on respiratory infections has been getting an increased interest. Tilmovet® is registered exclusively for veterinary use and primarily for acute respiratory diseases like several serotypes of *Actinobacillus pleuropneumoniae* or chronic respiratory diseases like *Mycoplasma spp., Pasteurella multocida , Bordetella bronchiseptica* and other bacteria sensitive to tilmicosin in pigs, poultry and cattle.

Structure and activity

Tilmicosin has a wide spectrum of activity against Gram-positive organisms of porcine, avian and bovine origin as well as some activity against Gram-negative micro-organisms. Cross-resistance between tilmicosin and other macrolide antibiotics and lincosamides has been observed. Tilmicosin may reduce the antibacterial activity of ß-lactam antibiotics.

Mode of action

Macrolide antibiotics are bacteriostatic compounds that reversibly bind to the 50S ribosome subunit and inhibit mRNA-directed protein synthesis of susceptible micro-organisms. The tilmicosin spectrum of activity includes *Actinobacillus pleuropneumonia, Mycoplasmata, Pasteurella, Bordetella* and Gram-positive bacteria and some Gram–negative germs.

Product categorization and use

Tilmovet® Medicated Premix is an oral medicated feeding stuff for weaned piglets and fattening pigs. It is available in different concentrations: 40, 100 and 200 g/kg. An oral administration of 1 kg of the veterinary medicinal product corresponds to 40, 100 or 200 g of tilmicosin active. The dose for pigs is 16 mg tilmicosin per kg body weight for a period of 15 days. Tilmovet® is also available as oral drinking water solution and is specifically suitable for therapeutic use, whereas the Medicated Premix for feeding stuff is ideally incorporated in controlling and therapeutic programs.

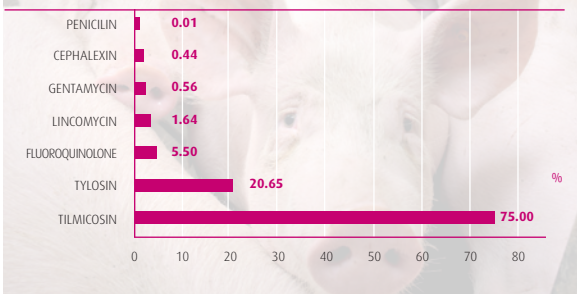
Pharmacokinetic and dynamics

Tilmicosin inhibits the bacterial protein synthesis in vitro and in vivo, without affecting the nucleic acid synthesis. It is mostly bacteriostatic and has a bactericidal effect on *Pasteurella spp.* Tilmicosin has a wide spectrum of activity against Gram-positive organisms and some Gram-negative micro-organisms, specifically those of the respiratory tract.

Absorption and distribution

When administered to pigs via the oral route at a dose of 16 mg/kg BW in the feed, tilmicosin moves rapidly out of the serum into areas of low pH. The highest concentration in the serum and maximum concentration in lung tissue are recorded on day 10 of medication.
Apart from high levels in the lungs and in lung tissue macrophages (see graph 1: relative concentrations), Tilmicosin is also distributed in the liver and kidney tissues. Tilmicosin is also known to concentrate in alveolar macrophages in swine, giving it an indirect effect on PRRSV.

Graph 1: Relative Concentration Of Antibiotics In Macrophages In Comparison To Extra Cellular Concentrations.



Tilmicosin: Die Fakten Von Dr. Manfred Stein.
Ref. Scorneaux, B. and Shryock, T.R. 1998, Intracellular accumulation, subcellular distribution and efflux of tilmicosin in swine phagocytes, JVPT 21(4):257-268.

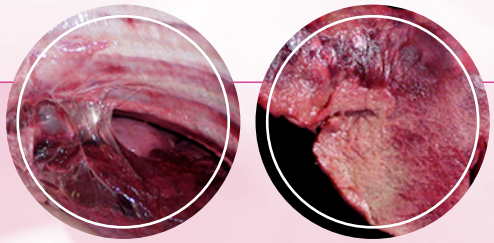
Elimination

Some metabolites are formed, the predominant one being identified as T1. The bulk of tilmicosin is excreted unchanged, although tilmicosin is excreted mainly via the bile into the faeces, but a small proportion is excreted via the urine.

Actinobacillus pleuropneumonia

Disease

Actinobacillus pleuropneumoniae (APP) is the causative agent of porcine pleuropneumonia, a serious and often fatal disease affecting swine of all ages. All age groups are susceptible, yet in chronically infected herds, pleuropneumonia is mainly diagnosed in fatteners and animals of 12 weeks of age. Pigs can be infected at ages of < 4 weeks, carrying the pathogen in the tonsils without clinical symptoms and without production of antibodies. At older ages, APP can reach the lungs and seroconversion can occur.



Transmission

It is believed that direct contact and nasal droplets within short distance are the main route of disease transmission, although a spread across pens has been seen in acute outbreaks (aerosol transmission, farm personnel).
Susceptible herds are mainly infected by asymptomatically chronically infected animals. Other risk factors are viral and bacterial infections, **stress moments** like weaning, crowding, moving, mixing and adverse climate conditions.

Symptoms

Typical symptoms in (per)acute cases are sudden high fever with apathy, lethargy and anorexia, rapidly followed by cardiac and vascular failure resulting in cyanosis of nose, ear, legs and/or the entire body. Sometimes, diarrhoea and vomiting is observed. In the terminal phase, severe respiratory distress (dyspnoea, coughing, open mouth breathing) can occur.

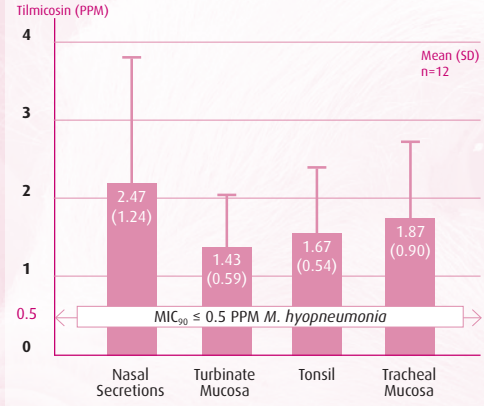
Associated diseases

APP is often complicated with severe PRRS infections. It is assumed that PRRSV infections are triggering APP infections. This combination causes continuous and tremendous losses with mortality rates between 4 and 10%, higher treatment costs in acute outbreaks and an increased feed conversion. Next to this, PRRSV gives rise to a number of reproductive failures (increased abortions, more mummified foetuses, stillborn and weak born piglets).

Interactions with bacteria

The host's defense effectiveness against pulmonary bacterial infections depends on the rapid clearance and its immune reaction and modulation due to direct or indirect antibiotic concentration in different tissues (see graph 3).

Graph 3:
Tilmicosin Concentrations Following *ad lib.* Exposure To Tilmicosin 400 PPM



Fossler, S., JW Moran, TD Thomson., Tilmicosin mode of action against Mycoplasma hyopneumoniae in swine proceedings, 17th IPVS Congress, 2002.

Tilmovet® and pneumonia

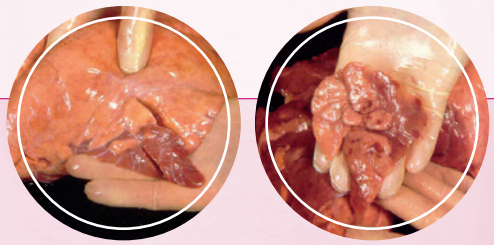
Tilmovet® treatments have a proven beneficial effect on contagious pleuropneumonia. An oral administration decreased the APP pressure in lungs (decreased lung lesions and inflammation) as well as the APP associated mortality. This had a positive impact on daily weight gain, feed conversion and clinical signs in all weight classes. A series of published studies clearly demonstrate that Tilmovet® can perfectly treat clinical outbreaks (reducing clinical signs, mortality and culled pigs) as well as prevent new disease cases. Tilmovet® lowers the possible risk of viral infection by making the macrophage non-permissive. In addition tilmicosin is reported to induce apoptosis in alveolar leucocytes and in this matter attenuate inflammation.

Macrolides are known to be an effective treatment against pulmonary bacterial infections. In general, this class of product has a series of therapeutic antibacterial effects and concentrates specifically in macrophages, other phagocytic cells, fibroblasts and tracheal and bronchial mucosa.
Tilmicosin was reported to inhibit in vitro PRRSV replication in alveolar macrophages. Also, the use of tilmicosin pretreatment of porcine alveolar macrophages significantly reduces replication of PRRSV in a dose dependent way. This results in a significant reduction of lymph node hypertrophy and lung lesions but also a reduced virus load in systemic circulation.

Mycoplasma hyopneumonia

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). Combined infections with *Pasteurella multocida* and/or *Actinobacillus pleuropneumoniae* result in more severe lesions compared to the single infections. Co- or subsequent infections are commonly found in field outbreaks of enzootic pneumonia.



Recommendations for treatment and management of pneumonia

The control of the APP infections requires a combination of management actions, prevention of crowding, mixing and adverse climate stable conditions, treatment and/or vaccination programs.

Tilmicosin is the right antibiotic for:

- Treatment of *Actinobacillus pleuropneumoniae*
- Treatment of *Pasteurella multocida*
- Treatment and managment of *Mycoplasma hyopneumoniae*.
- Treatment and management of PRDC.

Tilmovet®

Contraindications

Horses or other *Equidae*, must not be allowed access to feeds containing tilmicosin. Horses fed with tilmicosin medicated feeds may present signs of toxicity with lethargy, anorexia, reduction of feed consumption, loose stools, colic, distension of the abdomen and death. Do not use in case of hypersensitivity to tilmicosin or to any of the excipients Do not use in animals hypersensitive to tilmicosin and when there is resistance to tilmicosin or cross resistance to other macrolides like tylosin, erythromycin or lincomycin.

Special warnings

With regard to the management of respiratory disease outbreaks, it should be noted that acutely ill animals are likely to be inappetant and therefore require parenteral treatment.

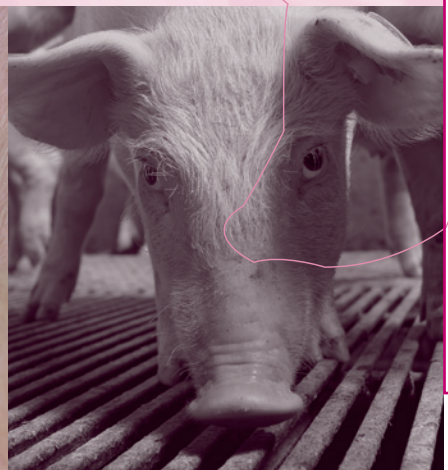
Special precautions for use in animals

Inappropriate use of the product may increase the prevalence of bacteria resistant to tilmicosin and may decrease the effectiveness of treatment with tilmicosin related substances.
Due to the likely variability (time, geographical) in the occurrence of the resistance of bacteria for tilmicosin, bacteriological sampling and susceptibility testing are recommended.

Cross-resistance between tilmicosin and other macrolide antibiotic has been observed. Use of the product should be based on susceptibility testing and take into account official, national and regional antimicrobial policies. Inappropriate use of the product may increase the prevalence of bacteria resistant to tilmicosin and may decrease the effectiveness of treatment with tilmicosin related substances.

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

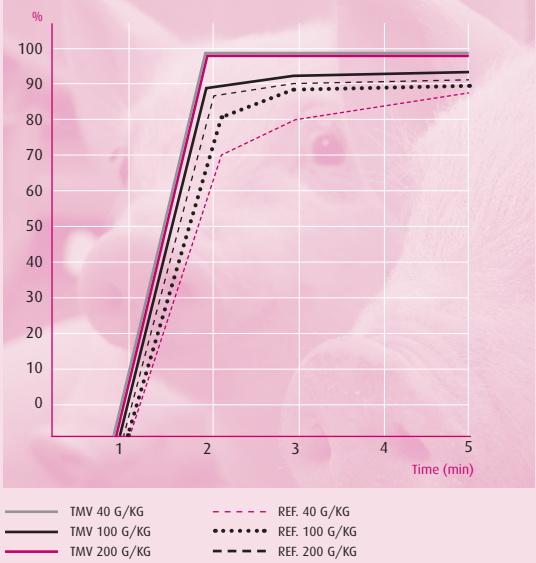
The handling of the product in case of known hypersensitivity to macrolide antibiotics must be avoided.
May cause sensitisation by skin contact. May cause skin and eye irritation. Avoid direct skin contact. Wear overalls, safety glasses and impervious gloves when mixing and handling the product. Wash affected parts if skin contact occurs. If accidental eye contact occurs, immediately rinse thoroughly with water. In case of accidental ingestion, or if you develop symptoms following exposure such as skin rash, seek medical advice immediately and show the package leaflet or the label to the physician. Swelling of the face, lips or eyes or difficulty with breathing are more serious symptoms and require urgent medical attention.
If the operations involve the risk of exposure to dust, wear either a disposable filter and half mask respirator conforming to European Standard EN149 or a non-disposable respirator to European Standard EN140 fitted with a filter to EN143. This warning is particularly relevant to on-farm mixing, where the risk of exposure to dust is likely to be enhanced.



Product specifications

Tilmovet® Medicated Premix for medicated feeding stuff has a yellowish to brown tan and is characterized by its free-flowing behavior. Tilmovet® Medicated Premix is meant for incorporation into feeding stuff only.

Graph 2: Comparative Dissolution Test: Tilmovet Medicated Premix Versus Competing Reference Tilmicosin Formulations



Stability

In accordance with the requirements of the Committee for medicinal products for veterinary use (CVMP), a number of stability tests of premix in feed were carried out, each at 200 and 400 ppm in:

- starter mash feed,
- mash feed,
- starter pelleted feed and
- pelleted feed.

Results obtained in the stability study in feed lead to the conclusion that the product has remained within the quality specifications after 3 months, the suggested validity period of the medicated feed, regardless of type of feed, pellet or mash.

In-use stability

In-use tests after opening of the original bags and under normal environmental conditions for 3 months, demonstrate that the characteristics of the product comply with the specification limits.

- No significant deviations in tilmicosin content and component composition values were found.
- No changes in the impurity profile were observed either.
- In terms of storage conditions, there is no need to take specific precautions, except dry storage.

Dissolution

Several dissolution tests have been performed and these demonstrated that all formulations had an immediate release of the active substance being between 99.34% and 99.9% for the different concentrations. Approximately 95% of the total content in tilmicosin was released in 10 minutes from all the formulations/concentrations. This is well above the dissolution rate of 85% after 15 minutes which is considered enough to guarantee bioavailability.

Homogeneity

Different homogeneity studies have been performed to verify the homogeneity of the Tilmovet® Medicated Premix in both mash and pellet feed after manufacturing (each at different levels of production). All samples showed standard deviations well below 5%, being the maximum percentage of deviation with regard to the mean, thus confirming the homogeneity.

To ensure thorough dispersion of the product, it should first be mixed with a suitable quantity of feed before being incorporated into the finished feed.

Amount(s) to be administered and administration route

One kg of Tilmovet® Medicated Premix corresponds to 40, 100 or 200 g of tilmicosin active, depending on the selected product. In all concentrations, the dose for pigs is 8- 16 mg tilmicosin per kg of body weight for a period of 15 to 21 days.

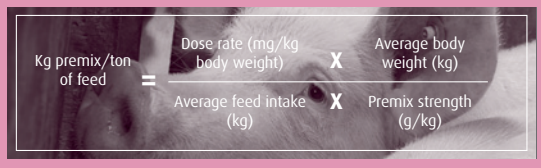
For prevention and treatment of respiratory disease in pig:

Pigs

- **8 to 16 mg tilmicosin per kg BW per day.**

Practical administration

For the preparation of the medicated feed, the body weight of the animals to be treated and their average feed consumption should be taken into account.
This consumption depends of age, state of health, breed and husbandry system.
In order to calculate the exact amount of premix to be added to the feed, use the following formula to achieve the target dose:



Withdrawal period(s)

Meat and offal

- Pigs: 21 days.

Shelf-life

- Shelf-life of the veterinary medicinal product as packaged for sale: 36 months.
- Shelf-life after incorporation into meal or pelleted feed: 3 months.
- Shelf-life first opening of the container: 3 months.

Incompatibilities

- Do not mix into feed containing bentonite.
- In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

Other species

- Tilmovet premix is also registered for rabbits.
- For further information please consult the species related brochure.

Packaging

Tilmovet® Medicated Premix for medicated feeding stuff has a yellowish to brown tan of free-flowing granular material. All existing formulations are packed in **5 and 20 kg bags**. The 200 g/kg formulation is also available in a **1 kg bag**. Check with your local Huvepharma representative which pack sizes are available in your region as this may vary.

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 cause sensitisation by skin contact. May cause skin and eye irritation. Avoid direct skin contact. Wear overalls, safety glasses and impervious gloves when mixing and handling the product. Wash affected parts if skin contact occurs. If accidental eye contact occurs, immediately rinse thoroughly with water. In case of accidental ingestion, or if you develop symptoms following exposure such as skin rash, seek medical advice immediately and show the package leaflet or the label to the physician. Swelling of the face, lips or eyes or difficulty with breathing are more serious symptoms and require urgent medical attention. If the operations involve the risk of exposure to dust, wear either a disposable filter and half mask respirator conforming to European Standard EN149 or a non-disposable respirator to European Standard EN140 fitted with a filter to EN143. This warning is particularly relevant to on-farm mixing, where the risk of exposure to dust is likely to be enhanced.

* *Used references can be obtained on demand.*
** *Tilmovet® medicated premix 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. For further information, consult your veterinarian surgeon and local country SPC.*
**** *Use medicines responsible- Legal Category: UK POM-V/IE POM.*

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