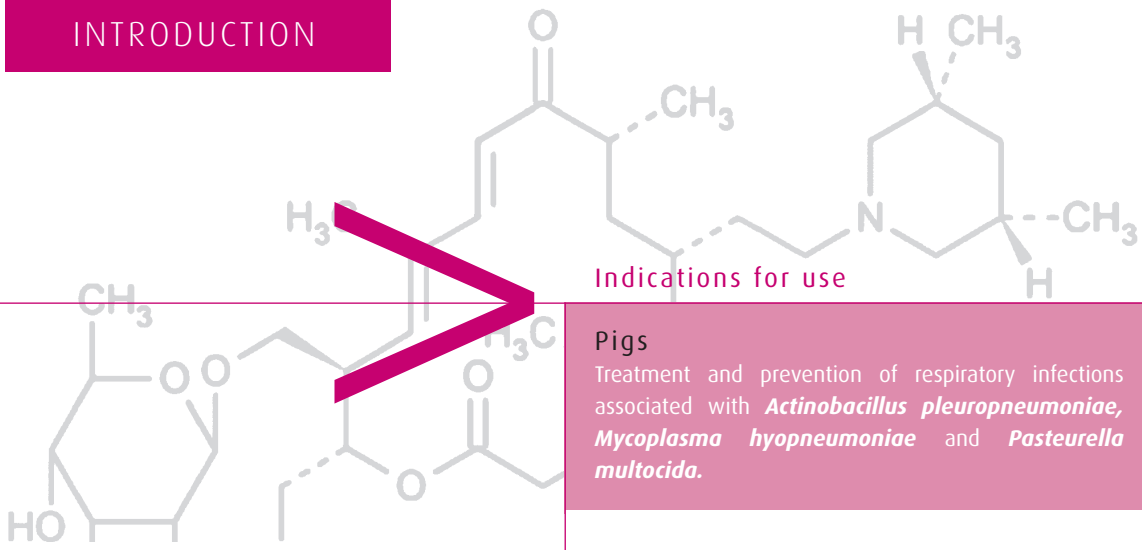
HUVEPHARMA®

# Tilmovet®

250 MG/ML CONCENTRATE FOR ORAL SOLUTION



## Indications for use

### Pigs

Treatment and prevention of respiratory infections associated with ***Actinobacillus pleuropneumoniae, Mycoplasma hyopneumoniae*** and ***Pasteurella multocida.***

## Origin of the molecule

Tilmovet® 250 mg/ml Concentrate for Oral Solution contains tilmicosin. It is a semi-synthetic macrolide antibiotic obtained from tylosin which is affecting bacterial protein. Macrolides have been used for decades as treatment for a wide range of infectious diseases, but their effect on respiratory infections have 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.* and *Pasteurella multocida* 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, Mycoplasma spp, Pasteurella*.

## Product categorization and use

Tilmovet® 250 mg/ml is an oral solution for pigs. An oral drinking water administration of 1 ml of the veterinary medicinal product corresponds to 250 mg of tilmicosin active. The dose for pigs is 6-8 ml per 100 kg of body weight.
Tilmovet® is also available as medicated premix.

## Pharmacokinetic and dynamics

When administered orally with drinking water, tilmicosin is rapidly absorbed and moving out of the serum into areas of low pH. This results in very low serum concentrations, yet tilmicosin levels are found in lung tissues as early as 6 hours after treatment initiation. Tilmicosin is also known to concentrate in alveolar macrophages in swine, giving it an indirect antiviral effect on PRRSV.
Tilmicosin is slightly, to moderately bound to plasma proteins (less than 30%). This is creating a high degree of lipid solubility which makes it widely distributed in body fluids and tissues.

## Absorption and distribution

Tilmovet® 250 mg/ml is quickly absorbed from the alimentary tract of pigs independent of age.

- Peak plasma concentrations are reached within 1 to 2 hours after administration.
- Tilmicosin can be found in all tissues, between 30 minutes and 2 hours after oral administration.
- Tilmicosin is distributed throughout the entire body, but highest concentrations were found in liver, kidney and lung tissue.
- TMS concentrates in the macrophages. A high intra/extra cellular ratio is reached. These intracelllular concentrations could serve as reservoir, helping to maintain concentrations in target tissues.

## Elimination

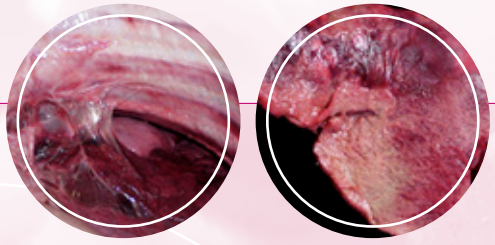
Elimination of tilmicosin from blood serum is relatively slow. In pigs, about 80% of tilmicosin is excreted in faeces and about 15% in urine.

# *Actinobacillus pleuropneumoniae*

## Disease

*Actinobacillus pleuropneumoniae* (APP) is the causative agent of porcine pleuropneumonia, a serious and often fatal disease affecting swine of all ages. Porcine contagious pleuropneumonia has been described worldwide (prevalence of country specific serotypes) with the industrialization of pork production being a contributing factor in the increased occurrence.

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 primary viral and bacterial infections, stress, 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.

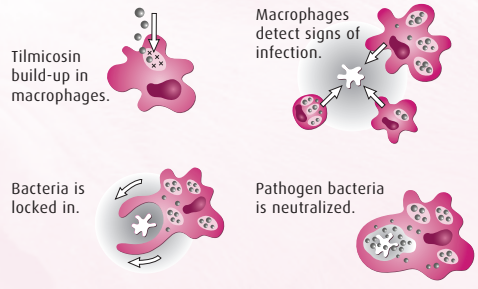
However, animals may die suddenly without any premonitory symptoms. Chronically infected animals show non-characteristic symptoms, but suffer mostly from a reduced appetite, decreased weight gain and increased feed conversion. Chronic infections can perfectly develop without symptoms of acute disease.

## Interactions with bacteria

In general, APP enters the lungs after inhalation as an aerosol and binds to cells of the lower respiratory tract. After colonization of the host's lung tissue, APP acquires nutrients for growth (iron, nickel and sugars) via pore forming exotoxins (APX's) that will lead to cell damage and eventually cell destruction.

The host's defense effectiveness against pulmonary bacterial infections depends on the rapid clearance, yet APP possesses several ways to escape the host's immunity and due to the ability to adapt easily to different environmental conditions, APP can survive during long periods in necrotic lung tissue and tonsils, resulting in carrier animals.

INTERACTION OF TILMOVET® WITH BACTERIA AND IMMUNE SYSTEM




## 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).

## Tilmovet® and pneumonia

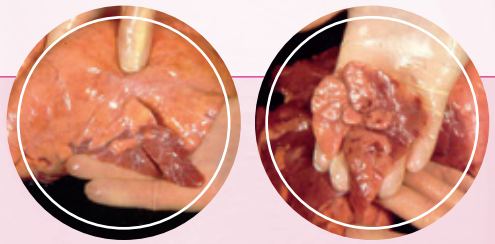
Tilmovet® treatments have a proven beneficial effect on contagious pleuropneumonia. An oral administration decreased the APP pressure in lungs (decreased lung lesions and inflammation) as well as the APP associated mortality. This had a positive impact on daily weight gain, feed conversion and clinical 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.

## *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).
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 prevention

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.

It is noteworthy that pathogen elimination in a herd is impossible, leaving room for bacterial shedding animals. However, controlled treatments during periods of risk may help to prevent an outbreak in fattening herds. Chronically infected herds may benefit from multiple treatment programs.

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.

Tilmovet®

### Contraindications

Do not use in case of hypersensitivity to the active substance or in cases of known resistance to tilmicosin. Do not use in horses.

### Special warnings

Tilmovet® 250 mg/ml must be diluted in drinking water before administration. Make sure to keep the product protected from light after reconstitution. Tilmovet® 250 mg/ml should not be administered by injection.
Due to likely variability (time, geographical) in susceptibility of bacteria to Tilmovet® 250 mg/ml bacteriological sampling and susceptibility testing is sound clinical practice to decide on the treatment approach. Underdosing and/or treating for an insufficient length of time are considered to increase tilmicosin resistance in bacteria and should be avoided at all times.

### Special precautions for use in animals

Due to the administration route and as water consumption depends on the clinical condition of the animal, the concentration of the product must be adjusted according to the water intake to ensure correct dosing. If this is not possible, then an alternative medication may be required. As animals with acute infections may have a reduced water and feed consumption, they should be treated with a suitable injectable veterinary medicinal product first. The sensitivity of bacteria to tilmicosin may have changed over time or geographically. The medicated water should be freshly prepared every 24 hours.
Do not allow horses or other equines access to drinking water containing tilmicosin.
In case of use during pregnancy and lactation, the veterinarian must first assess the risk/benefit.

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

People with known hypersensitivity to tilmicosin should avoid contact with the product. Any skin and ocular contact may cause irritation or sensitization. In case of skin or eye contact, rinse abundantly with fresh water. If irritation persists and in case of accidental ingestion, seek immediate medical advice or call a poison centre (possible dangers linked to disturbances in cardiac conduction). Always wash hands after use.

## Product specifications

Tilmovet® 250 ml/ml concentrate for Oral Solution has a clear yellow to amber color and is meant for oral use only. As the product is sensitive to direct sunlight, a white, high density polyethylene (HDPE) bottle with marker window was selected to provide maximal protection and guaranteed stability.

## Solubility

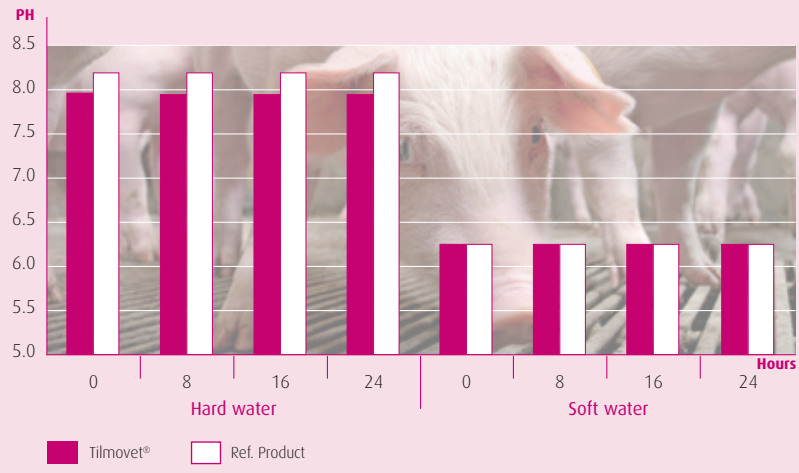
Tilmovet® 250 mg/ml is a concentrated solution and is perfectly soluble in regular tap and or pumped water regardless of temperature and water hardness.
It is suitable for use in automatic dosing pumps and water tank applications. In both systems, a concentrated solution can be used, as it will be further diluted in the automatic water supply lines.

## Stability

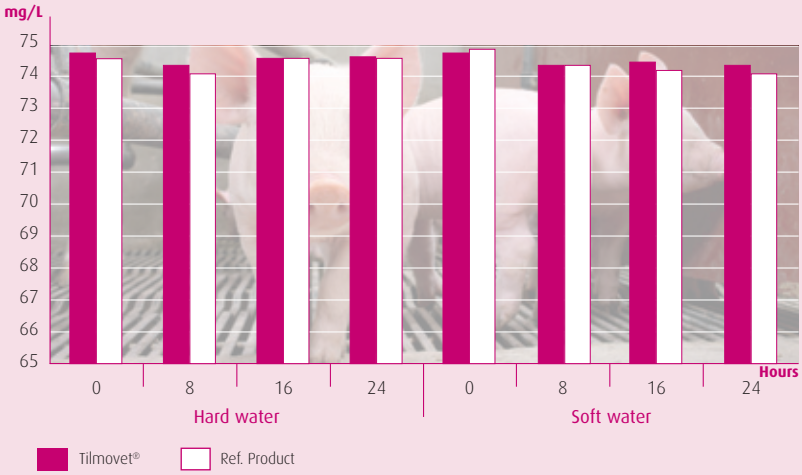
In accordance with the current Committee for medicinal products for veterinary use (CVMP), the stability of medicated drinking water containing Tilmovet® 250 mg/ml was tested using two types of water. Stability was tested in hard (pH 8-9) and soft water (pH 5-7) and controlled for a period of 24 hours at 25°C. No indication of any significant change or variability was found.

COMPARISON OF TILMOVET® WITH REFERENCE PRODUCT USING A SOLUTION OF 75 MG/L TILMICOSIN

STABILITY AND PH




QUANTIFICATION OF TILMICOSIN



## Amount(s) to be administered and administration route

An oral drinking water administration of 1 ml of the veterinary medicinal product corresponds to 250 mg of tilmicosin. The dosages are as follows:

## Pigs

**15-20 mg tilmicosin per kg BW for 5 days, i.e. 6-8 ml of the veterinary medicinal product for 100 kg BW for 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. In order to provide the required amount of active substance in mg per liter drinking water, the following calculation should be made:

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

Below an overview as example:

| | Tilmovet® 250 mg/ml dose in ml/animal | |
|---|---|---|
| Weight in kg | **20** mg/kg/BW | **15** mg/kg/BW |
| 20 | 1.60 | 1.20 |
| 40 | 3.20 | 2.40 |
| 60 | 4.80 | 3.60 |
| 80 | 6.40 | 4.80 |

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

If signs of disease do not significantly improve within 3 to 5 days, the diagnosis should be re-evaluated and treatment changed.

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: 14 days.

### Shelf-life

- Shelf-life of the veterinary medicinal product as packaged for sale: 24 months.
- Shelf-life after first opening the immediate packaging: 3 months.
- Shelf-life after dilution in drinking water according to directions: 24 hours.

## Other species

- Tilmovet® 250 mg/ml is also registered for **Chickens, Turkeys and Calves**.

  For further information please consult the species related brochure.

## Packaging

Tilmovet® 250 mg/ml concentrate for Oral Solution has a clear yellow to amber color and is meant for oral use only.
As the product is sensitive to direct sunlight, a white, high density polyethylene (HDPE) **bottle of 960 ml** with marker window was selected to provide maximal protection and guaranteed stability.
The bottle has a white tamper-evident cap.


**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.*
** *Tilmovet®250 mg/ml 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.*
*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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