HUVEPHARMA®

# Tilmovet®

250 MG/ML CONCENTRATE FOR ORAL SOLUTION

# INTRODUCTION

## Indications for use

### Calves

Treatment and prevention of respiratory infections associated with ***Mannheimia haemolytica, P. multocida, Mycoplasma bovis*** and ***M. dispar.***

## 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 synthesis. 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 respiratory diseases associated with *Mannheimia haemolytica, Mycoplasma spp.* and *Pasteurella multocida* and other bacteria sensitive to tilmicosin in calves, pigs and poultry.

## Structure and activity

Tilmicosin has a wide spectrum of activity against Gram-positive organisms *Mycoplasma spp.* of bovine, porcine and avian 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. The tilmicosin spectrum of activity includes *Mycoplasma spp.* Gram-positive bacteria and some Gram – negative germs.

## Product categorization and use

Tilmovet® 250 mg/ml is an oral solution for cattle. An oral drinking water administration of 1 ml of the veterinary medicinal product corresponds to 250 mg of tilmicosin active. The dose for calves is 1 ml per 20 kg of body weight two times per day for 3-5 days.
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 and remains at the therapeutic level up to 60 hours from the last dose.
Tilmicosin is slightly, to moderately bound to plasma proteins (less than 30%) and has 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 calves independent of age.

- Peak plasma concentrations are reached within 1 hour 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.

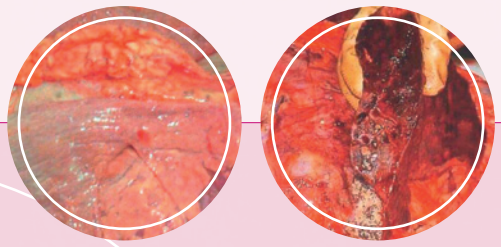
## Elimination

Elimination of tilmicosin from blood serum is relatively slow. In calves, about 70% of tilmicosin is excreted in faeces and about 20% in urine.

# *Bovine respiratory disease (BRD)*

## Disease

The bovine respiratory disease complex (BRDC; also called shipping fever or enzootic bronchopneumonia) is a multi-factorial disorder frequently seen in calves and young cattle. The disease causes increased death losses as well as medication costs, labor and production losses. Causes for BRD are multiple and complex, but in most cases factors such as **stress** (transport related, temperature variations, etc.), high stocking concentrations, poor ventilation and **viral** and **bacterial infections** are almost always involved. In cattle, *Mannheimia haemolytica sensu lato* and *Pasteurella multocida*, frequently secondary to viral infections or infections with *Mollicutes* infections (mostly *Mycoplasma bovis*, *Mycoplasma dispar* and *Ureuplasma diversum*), are often causing BRD. *M. haemolytica sensu lato* can cause bronchopneumonia as a primary pathogen.



## Epidemiology

*M. haemolytica* and *P. multocida* are frequently found without causing any infection. Under stress, the animal's defense mechanisms may be overcome and an exponential increase of their incidence in the upper respiratory tract may be found.

A colonization of the lower respiratory tract is the result of inhaling fluid drops containing these bacteria (endogenic infection). Calves excreting high numbers of these agents can be the source of infection for other calves (exogenic infection).

In 75% of animals suffering from chronic respiratory disease and 66% of animals suffering from acute respiratory disease, signs of *Mycoplasma spp.* (mostly *M. bovis*) infection are being found.

## Transmission

Aspiration of infected milk and contact with infected calves are believed to be the major transmission routes. Since the infection is often persistent, these animals can excrete the bacterium during a long period.

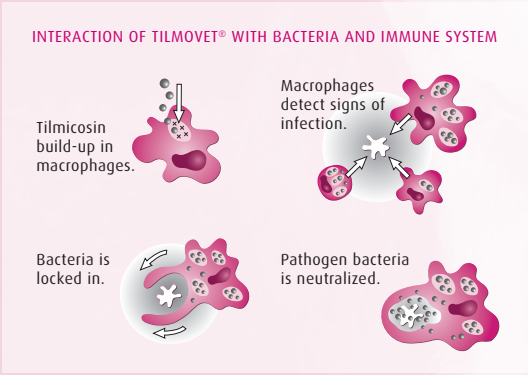
## Symptoms

General symptoms such as lethargy, fever and anorexia are combined with respiratory symptoms such as varying degrees of breathing difficulties and noise, rapid breathing, open mouthed breathing. The most common signs of BRD are nasal and eye discharges, coughing, decreased appetite, depression, droopy ears and death.

Acute respiratory disease caused by *M. haemolytica* and/or *P. multocida* will reveal a fibrinous, necrotizing lobular bronchopneumonia, with or without fibrinous pleuritis. Infection with *M. bovis* is mainly characterized by exudative bronchopneumonia and extensive fibrosis, even though lesions of coagulative necrosis and abscessation have been described.

## Interactions with other pathogens

Even though *M. haemolytica* and *P. multocida* are opportunistic bacteria, gaining access to the lower respiratory tract when immunologic defenses are comprised, several virulence factors have been described that might contribute to disease in calves (e.g. LPS, endotoxin, leukotoxin).




## Recommendations for prevention

There are two major areas of attention, i.e. management and vaccination. Of these two, management can already mean a significant change. All possible **causes of stress** should be eliminated or at least reduced during the entire period of processing, vaccinating, etc. Simple measures can lead to serious improvements, e.g. avoid the mixing of cattle from different sources, arrange the pens in a way that the animals have close access to feeders and water, keep the number of animals down to a minimum, etc. In general, hygiene and bio-security measures, supplemented with adjusted ventilation, will lower or even eliminate predisposing factors.

Vaccination is also often used to attempt BRD prevention, but despite intense research, a vaccine that confers a 100% protection is still missing.

## Recommendations for treatment

There are a large number of antimicrobial agents that are approved for the treatment of respiratory disease in cattle. Veterinarians having to select a particular agent to treat a diagnosed infection will be influenced by case-specific acquired resistance, volume and safety of administration and slaughter- or milk withdrawal period.

Recent guidelines mention macrolides (tilmicosin), (oxy) tetracyclines, spectinomycin and florfenicol as the first choice antimicrobials for treating bovine pneumonia. Macrolides, tetracyclines, florfenicol and fluoroquinolones have the advantage of also being active against *Mycoplasma sp*. thus providing a better protection and giving better results.

In case of inadequate response to the treatment, the antimicrobial agent should not be replaced earlier than 48 hours after the start of the treatment, allowing the chemotherapeutic to reach effective tissue concentrations.

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 or milk replacer before administration. Make sure to keep the product protected from light after re-constitution. 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. Under-dosing 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. The medicated milk replacer should be prepared fresh every 4 hours. Do not allow horses or other equines access to drinking water or milk replacer 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 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 with marker window was selected to provide maximal protection and guaranteed stability.

## Solubility

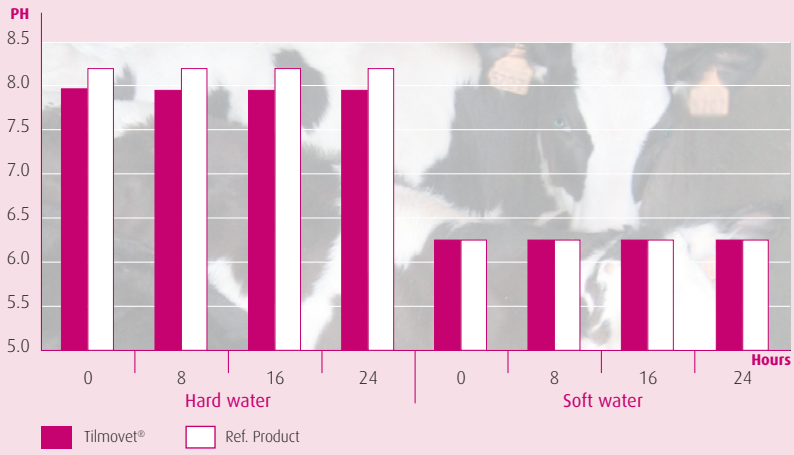
Tilmovet® 250 mg/ml is a concentrated solution and is perfectly soluble in regular tap and or pumped water regardless of temperature and water hardness. It is suitable for use in automatic dosing pumps and water tank applications. In both systems, a concentrated solution can be used, as it will be further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

## Stability

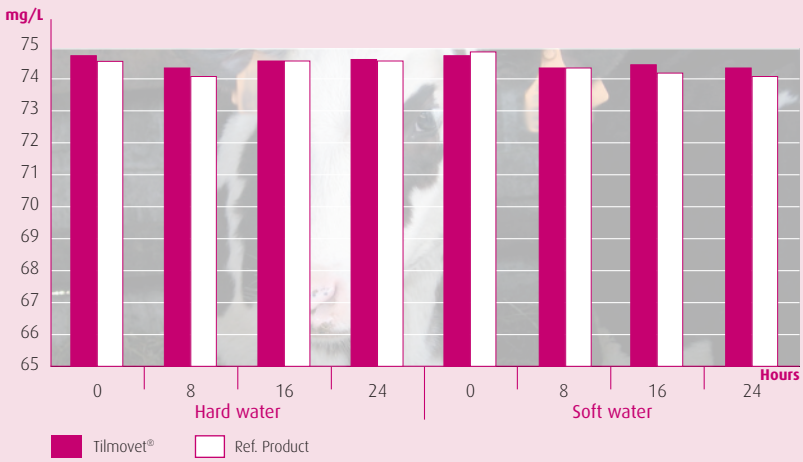
In accordance with the current Committee for medicinal products for veterinary use (CVMP), the stability of medicated drinking water containing Tilmovet® 250 mg/ml was tested using two types of water. Stability was tested in hard (pH 8-9) and soft water (pH 5-7) and controlled for a period of 24 hours at 25°C. No indication of any significant change or variability was found. Stability testing of Tilmovet® 250 mg/ml in milk replacer did not reveal any signs of change or variability.

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 or milk replacer administration of 1 ml of the veterinary medicinal product corresponds to 250 mg of tilmicosin. The dosages are as follows:

### Calves

**12.5 mg tilmicosin per kg BW two times per day for 3-5 days, i.e. 1 ml of the veterinary medicinal product for 20 kg BW two times per day for 3-5 days.**

## Practical administration

For the preparation of the medicated water and/or milk replacer, the body weight of the animals to be treated and their actual daily water consumption should be taken into account. The medicated drinking water should be prepared fresh every 24 hours using only clean water. The medicated milk replacer should be prepared fresh every 4 hours using only clean water.

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 | **12.5** mg/kg/BW: twice a day |
| 100 | 5.00 |
| 110 | 5.50 |
| 130 | 6.50 |
| 140 | 7.00 |
| 165 | 8.25 |

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

- Calves: 42 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 **Pigs**, **Chickens** and **Turkeys**.

  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.

* *MA number: UK: Vm 30823/4001, IE: VPA 10782/014/001*
** *Legal Classification: IE Legal category=POM, UK legal category=POM-V*
*** *Use medicines responsibly*
**** *For further information consult your veterinary surgeon and local country SPC.*

HUVEPHARMA®

HUVEPHARMA EOOD • 3a NIKOLAY HAYTOV STR. • 1113 SOFIA • **BULGARIA** • P +359 2 862 5331 • F +359 2 862 5334 • SALES@HUVEPHARMA.COM
HUVEPHARMA N.V. • UITBREIDINGSTRAAT 80 • 2600 ANTWERP • **BELGIUM** • P +32 3 288 1849 • F +32 3 289 7845 • CUSTOMERSERVICE@HUVEPHARMA.COM

Til.250.calves.05.0216.EN005/Novis