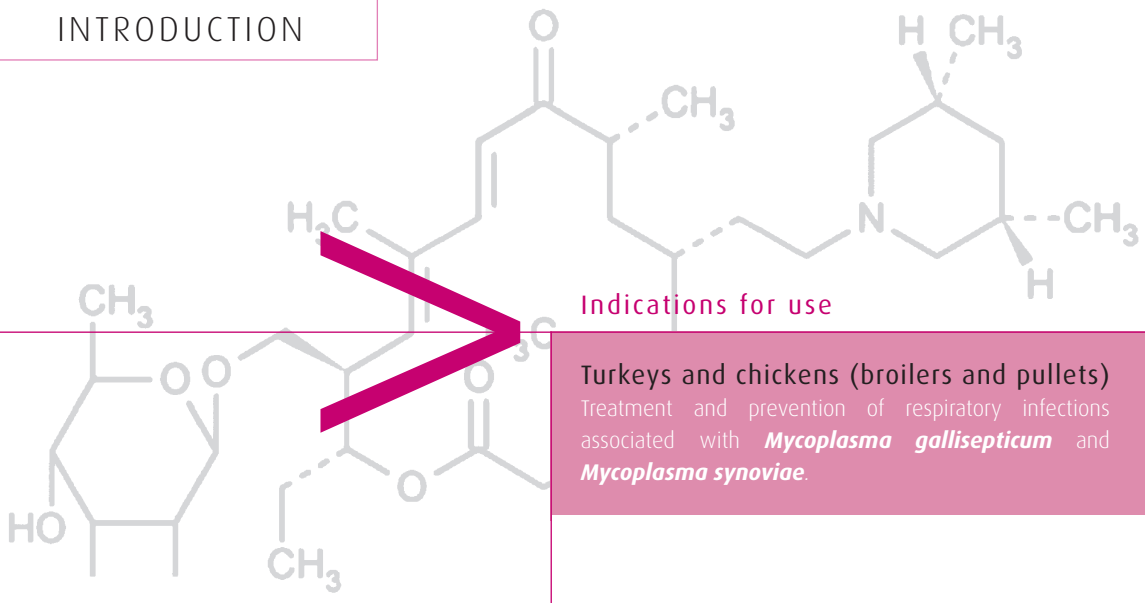
HUVEPHARMA®

Tilmovet®

250 MG/ML CONCENTRATE FOR ORAL SOLUTION



Indications for use

Turkeys and chickens (broilers and pullets)
Treatment and prevention of respiratory infections associated with ***Mycoplasma gallisepticum*** and ***Mycoplasma synoviae***.

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 *Mycoplasma spp.* and other bacteria sensitive to tilmicosin in poultry and cattle.

Structure and activity

Tilmicosin has a wide spectrum of activity against Gram-positive organisms of 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 lessen 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 *Mycoplasma gallisepticum* and *Mycoplasma synoviae* and Gram-positive bacteria and some Gram–negative germs.

Product categorization and use

Tilmovet® 250 mg/ml is an oral solution for turkeys and chickens (broilers and pullets). The use of Tilmovet® in layers producing eggs for human consumption is prohibited. An oral drinking water administration of 1 ml of the veterinary medicinal product corresponds to 250 mg of tilmicosin active. The dose for chickens is 6-8 ml per 100 kg of body weight. The dose for turkeys is 4-11 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 and pooled air sac tissue as early as 6 hours after treatment initiation. 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.

- Peak plasma concentrations are reached within 1 to 3 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.

Elimination

Elimination of tilmicosin from blood serum is relatively slow. In birds, tilmicosin levels decrease slowly, keeping the character appropriate to antibiotic with continuous effect.

Mycoplasma gallisepticum

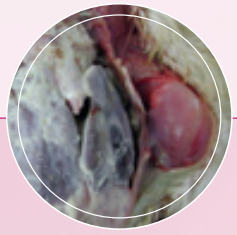
Disease

Mycoplasma gallisepticum (Mg) is the causative agent of Chronic Respiratory Disease (CRD) in chickens and infectious sinusitis in turkeys. Infection with *Mycoplasma gallisepticum* will predispose birds to other infections like *Escherichia coli* or *Ornithobacterium rhinotracheale*. Infections with Mg alone or in combination with complicating factors will lead to important economic losses due to reduced growth, reduced feed and egg-producing efficiency, increased mortality and condemnations in the slaughterhouse.

Mycoplasma gallisepticum infected chicken flocks will suffer from respiratory symptoms, decreased performance and increased condemnations at processing. Breeders will suffer from decreased production efficiency.

In turkeys *Mycoplasma gallisepticum* causes infectious sinusitis inducing sinusitis, pneumonia and airsacculitis. Clinical signs 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.

The severity of clinical signs is strongly influenced by concurrent viral or bacterial infections and environmental factors.



Epidemiology and transmission

The epidemiology of the Mycoplasma infections is influenced by many factors. *Mycoplasma gallisepticum* strains may differ in virulence, serological response and tissue tropism. An important route of spreading is the **vertical transmission** from the breeder flocks to the progeny. Mycoplasma bacteria have been recovered from oviducts, semen, embryos and also the vitelline membranes of fresh eggs.

Mycoplasma bacteria are **horizontally transmitted** through direct contact with infected carrier chickens or turkeys. Once the infection is present in a flock, most frequently all animals in the same airspace will become infected.

Because of its ability to penetrate and survive within host cells and thus evading the host's immune system, Mycoplasma is able to chronically infect the host. The disease can also be transmitted indirectly by airborne droplets, dust, mechanical or natural infected vectors such as wild birds.

Risk of infection can increase due to environmental factors such as high ammonia concentrations in the surroundings, concurrent respiratory infections and impaired immunity. Mycoplasma is able to survive in the environment and therefore can also be indirectly transmitted through contact with contaminated equipment, crates, feed, water, litter, egg trays, etc.

Interactions with bacteria

By adhering to the internal lining of the respiratory cells, *Mycoplasma gallisepticum* will damage the cells, making them more susceptible to other pathogens such as viruses and bacteria. Infections in combination with *Escherichia coli* may result in chronic respiratory signs, also known as Chronic Respiratory Disease (CRD). Concurrent infections like *Ornithobacterium rhinotracheale* or *Pasteurella multocida* are known to aggravate the clinical signs and the duration of *Mycoplasma gallisepticum* infections. Infected birds will have more severe reactions on viral respiratory pathogens or respiratory vaccines.

Recommendations for treatment and prevention

Available methods for *Mycoplasma gallisepticum* control are mostly based upon surveillance of breeding flocks via serological monitoring, PCR detection or Mycoplasma isolation techniques. Laying flocks are considered to be an important reservoir of Mycoplasma infections, especially in multi-age flocks and areas with high infection pressure. Vaccination generally results in protection against vertical transmission, reduction of clinical signs and drops in egg production. However, vaccination with live vaccines is insufficient to prevent completely the horizontal spreading of *Mycoplasma gallisepticum*. Medication is a very important tool to control the clinical signs and the transmission of Mycoplasma infections. To avoid development of antibiotic resistance by other bacteria it is advised to use Mycoplasma selective antibiotics like Tilmovet® (tilmicosin) over broad-spectrum antibiotics.

Mycoplasma synoviae

Disease

Mycoplasma synoviae is the cause of upper respiratory infections and infectious synovitis in poultry. There is considerable variation in the ability of these strains to cause disease and in the location of the lesions (respiratory tract or joints).
They most frequently induce subclinical upper respiratory infections. Concurrent diseases like Infectious Bronchitis virus, Newcastle Disease, *Escherichia coli* or bad environmental conditions will aggravate the lesions and the clinical signs, resulting in more severe respiratory problems and drops in egg production. Progeny of *Mycoplasma synoviae* infected breeders will suffer from reduced feed intake and weight gain and higher percentages of condemnations in the slaughterhouse. In layers, the egg production may be affected. Lesions seen in the respiratory form of the disease are mostly restricted to several degrees of airsacculitis. Acute signs of arthritogenic strains will consist of swelling around the joints which can be infected, lameness and retarded growth. Animals have a slow recovery and usually infections persist within the flock. *Mycoplasma synoviae* induced lesions in the joints will consist of synovitis and inflammation of synovial membranes of the tendon sheets, joints and keel bursa.

Transmission and prevention

Mycoplasma synoviae can be transmitted vertically (from breeders to progeny) and horizontally. Horizontal transmission occurs by direct and indirect contact between *Mycoplasma* infected animals, equipment, human beings or naturally infected wild birds. Prevention of infections will therefore include stringent biosecurity measures to avoid contact between these possible threats.

Treatment recommendations

Suitable antibiotic medication is of value in the prevention and treatment of respiratory and joint lesions in infected flocks.

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. 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. Do not allow horses or other equines access to drinking water containing tilmicosin. Do not use in pullets and laying hens producing eggs for human consumption.

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

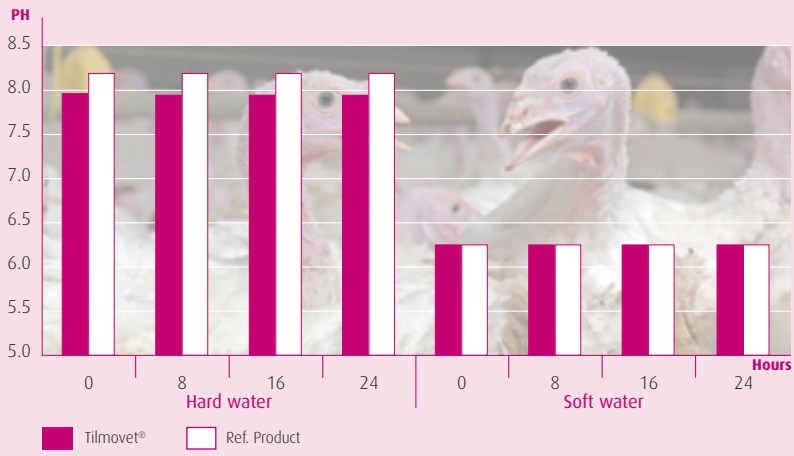
Tilmovet® 250 mg/ml is a concentrated solution and is perfectly soluble in regular tap and or pumped water regardless of temperature and water hardness. It is suitable for use in automatic dosing pumps and water tank applications. In both systems, a concentrated solution can be used, as it will be further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

Stability

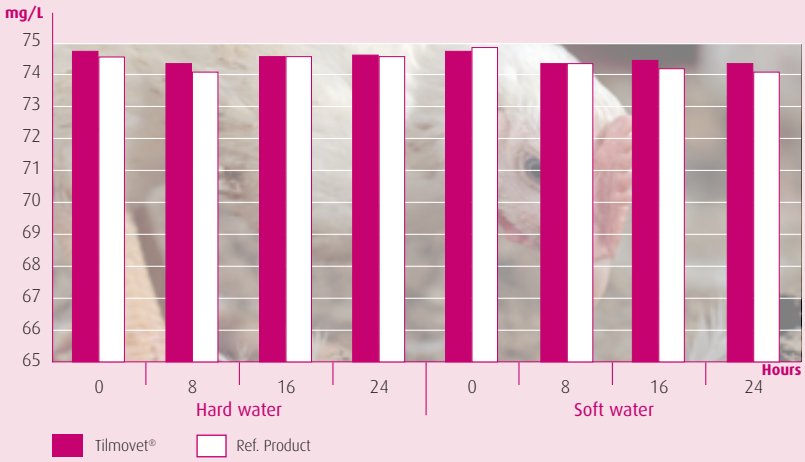
In accordance with the current Committee for medicinal products for veterinary use (CVMP), the stability of medicated drinking water containing Tilmovet® 250 mg/ml was tested using two types of water. Stability was tested in hard (pH 8-9) and soft water (pH 5-7) and controlled for a period of 24 hours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

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

STABILITY AND PH



QUANTIFICATION OF TILMICOSIN



Amounts 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:

Chickens (broilers, pullets)

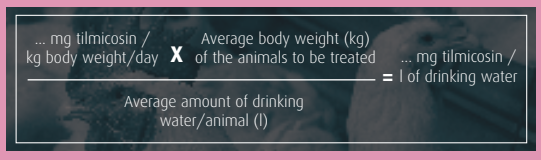
15-20 mg tilmicosin per kg BW for 3 days, i.e. 6-8 ml of the veterinary medicinal product for 100 kg BW for 3 days.

Turkeys

10-27 mg tilmicosin per kg BW for 3 days, i.e. 4-11 ml of the veterinary medicinal product for 100 kg BW for 3 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:



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

Below an overview as example:

Chickens	Tilmovet® 250 mg/ml dose in ml	
Dose/mg/LW	**15 mg/kg**	**20 mg/kg**
Weight in kg 100	6	8
250	15	20
500	30	40
1,000	60	80

Turkeys	Tilmovet® 250 mg/ml dose in ml	
Dose/mg/LW	**10 mg/kg**	**27 mg/kg**
Weight in kg 100	4	11
250	10	27
500	20	54
1,000	40	110

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.*
** 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.*

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

- Broilers: 12 days.
- Turkeys: 19 days.

Eggs: not permitted for use in laying birds producing eggs for human consumption.

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 **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 240 ml** was selected to provide maximal protection and guaranteed stability.

HUVEPHARMA®

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