Tilmovet®

250 mg tilmicosin/ ml
Concentrate for oral solution

Protect at an early age

HUVEPHARMA®
We add performance to your business

INTRODUCTION

Tilmovet® contains tilmicosin, a semi-synthetic macrolide antibiotic obtained from tylosin, which is affecting bacterial protein synthesis.

Tilmovet® is registered exclusively for veterinary use and primarily for respiratory diseases associated with *Mycoplasma spp.* and other bacteria sensitive to tilmicosin in poultry, pigs and cattle.

Pharmacokinetics

When administered orally with drinking water, tilmicosin is rapidly absorbed and moving out of the serum into areas of low pH, leading Tilmovet® concentrations to being **20-30 times higher in lung and air sacs** compared to plasma concentrations.

Tilmovet® is slowly excreted, giving Concentrations of > 1 µg/ in lungs and air sacs up to 5 days after termination of the treatment.

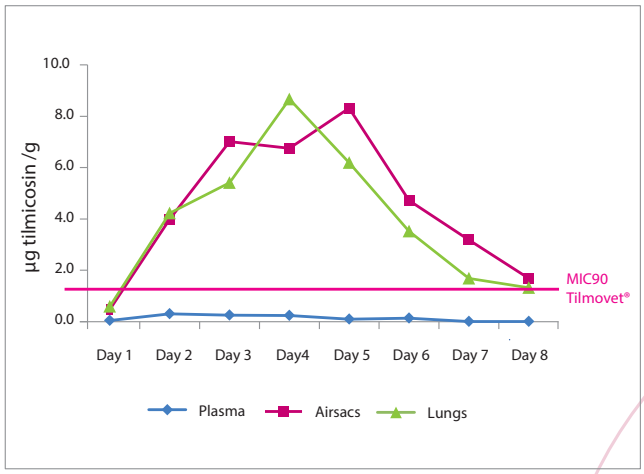


Figure 1. concentrations of Tilmovet in plasma, lung and air sacs after treatment for 3 days with 15 mg/ kg bodyweight Tilmovet® oral solution in the drinking water during the light period

Indications for use

Turkeys and chickens (broilers and pullets)

Treatment and prevention of respiratory infections associated with *Mycoplasma gallisepticum* and *Mycoplasma synoviae.*

Pharmacodynamics

Tilmicosin is especially active against *Mycoplasma spp.* and Gr-respiratory pathogens.

Pathogen	Number of isolates	MIC 50	MIC 90	Range	Reference	Breakpoint
Mycoplasma gallisepticum	*5*	<0.12	<0.12	0.12	unpublished layer data	≥32
Mycoplasma synoviae	*17*	0.5	1	0.015->1	Vereecken *et al.*, unpublished	≥32
	17	0.03	0.06	0.015->0.125	Landman *et al.*, 2008	≥32
Ornitobacterium rhinotracheales	*35*	2	32	2->32	Vereecken *et al.*, 2011	≥32
Gallibacterium anatis	*25*	8	32	2->64	Vereecken *et al.*, 2015	≥32

susceptible potentially resistant

Figure2. MIC's of some respiratory poultry pathogens

The pathogenic avian *Mycoplasma* spp., identified up to now, are:

- *M. gallisepticum,*
- *M. synoviae,*
- *M. meleagridis*
- *M. iowae*

and have been negatively affecting commercial poultry production for many years. The poultry industry and scientific community have made great strides in increasing the knowledge of the biology of these bacteria since they were first identified, but much is still to be revealed.

Mycoplasmas are small bacteria that lack:

- a cell wall
- certain metabolic pathways

which are both important targets for antibiotics.

Mycoplasmas were often considered to have a limited survival time outside the host. However, some recent data show that animal *Mycoplasma* species can survive for variable time periods outside the host, depending on the species, moisture, pH, presence of organic material and temperature. Some species have been shown to survive for 50 to 150 days at 4°C in liquid media and from 7 to 14 days under dry conditions at 30°C. Recently *M. synoviae* was shown to survive for 9 days on synthetic materials (Abolnik et al., 2014). The presence of persistently infected populations (e.g. backyard and wild birds) significantly contributes to the biosecurity of surrounding flocks being continually challenged. These are important reasons why *Mycoplasma* is still a major problem in the poultry industry. Secondly, antigenic variation and intracellular location of *Mycoplasma spp.* help the pathogen to evade the immunity system, leading to chronic infected animals and the fact that vaccines can in the best case scenario only help to reduce production losses and clinical symptoms.

The current approaches to control avian *Mycoplasma* include:

- continuous surveillance (see monitoring)
- quarantine measures,
- medication,
- vaccination,
- elimination of infected breeding flocks.

Once a flock is infected or vaccines are unable to control Mycoplasma, antibiotics are still required.

Clinical signs:

Mycoplasma gallisepticum	***Mycoplasma synoviae***
Respiratory	**Respiratory**
• Sneezing • Coughing • Conjunctivitis, sinusitis	• More susceptible to viral infections and reaction on vaccination (IB/ NCD)
Poor performance	**Arthritis**
• Growth • Reduced egg production • Decreased hatchability	• Synovitis
Sometimes only mild symptoms	**EAA = Egg Apex abnormalities**
• Except in case of 2nd infections	

Picture1. Arthritis caused by Mycoplasma synoviae

Picture2. Egg Apex Abnormalities caused by Mycoplasma synovia

Monitoring:

Diagnostic testing and program depends on:

- Type of flock
- Reason for testing
- Company policy
- Export requirements
- Financial constraints

Antibody detection:

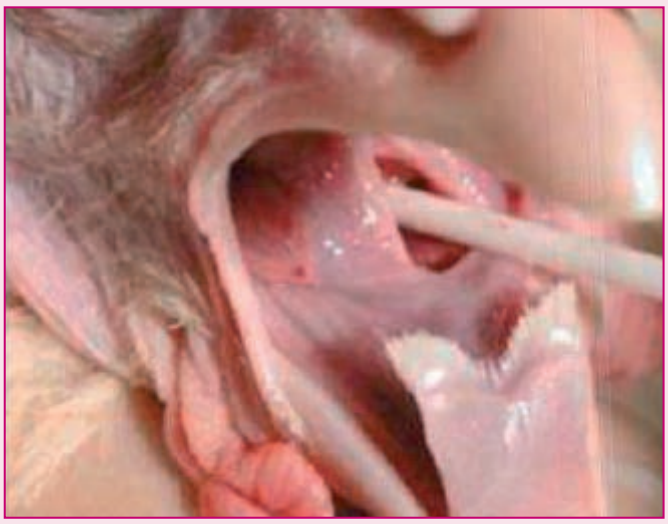
- Rapid Plate agglutination
- Haemagglutination Inhibition
- ELISA (Enzyme Linked Immunosorbent Assay)

Please contact your diagnostic supplier for correct interpretation and use.

PCR

- Shows presence of DNA
- Very sensitive
- Easy transport to lab with FTA cards
- Positive / negative
  - Evaluation of Mycoplasma status: positive-negative
  - Day olds: evaluation breeder flock program

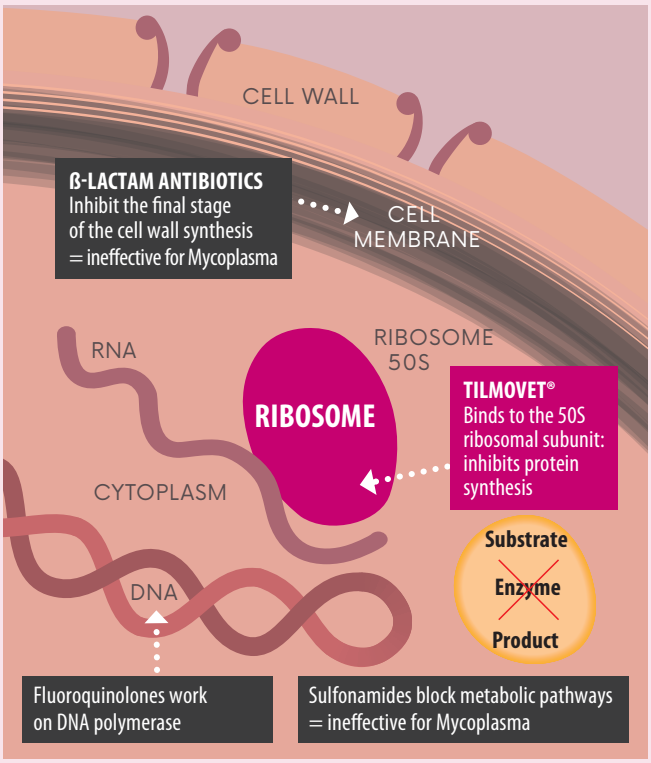
Please see sampling protocol and contact your veterinary surgeon or the Huvepharma® technical team for correct interpretation and advice.



Picture 3. Tracheal Swab for PCR testing

MYCOPLASMA CONTROL AND TREATMENT PROGRAM WITH TILMOVET® 250 mg/ml

Why Tilmovet®?



The most important considerations for a control program are:

1. Treat long enough 3-5 days
2. Administer daily dose as much as possible over 24 hours. NO PULSE dosing!
3. In high risk environment: increase treatment frequency, not the dose.

Low risk: 3-5 days	**every 28 days**
Medium risk: 3-5 days	**every 21 days**
High risk: 3-5 days	**every 14 days**

Dosing:

Challenge study using a recently isolated *Mycoplasma gallisepticum* strain (MG). (Europe, MIC value of < 0,015 µg/ml for tilmicosin).

Two treatment groups received Tilmovet® 250 mg/ml in the drinking water for 5 days, starting 1 day post challenge:

- Tilmovet®: 10 mg tilmicosin /kg bodyweight (BW) for 5 days.
- Tilmovet®: 20 mg tilmicosin /kg bodyweight (BW) for 5 days.
- Infected Untreated Control

Clinical and macroscopic scoring of respiratory signs and lesions were measured.

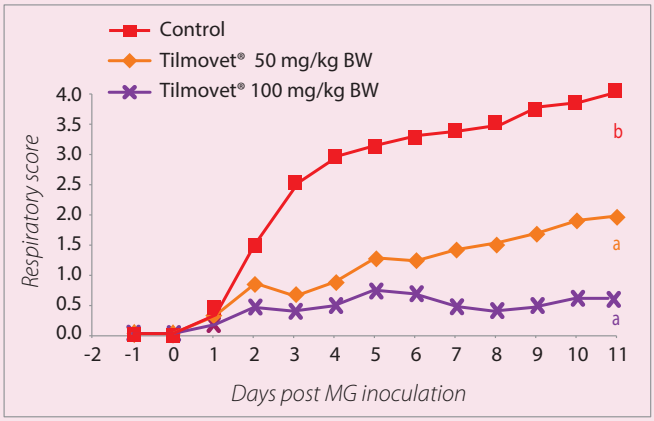


Figure 3. Mean respiratory scores (scoring system 0-4)

Conclusion

- For control of Mycoplasma a total dose of 50 mg Tilmovet® /kg bodyweight is recommended, divided over 3-5 days:
  - 10 mg Tilmovet®/ kg BW for 5 days
    or
  - ~ 15 mg Tilmovet® /kg BW for 3 days
- For treatment of Mycoplasma 20 mg Tilmovet® /kg bodyweight for 5 days is recommended

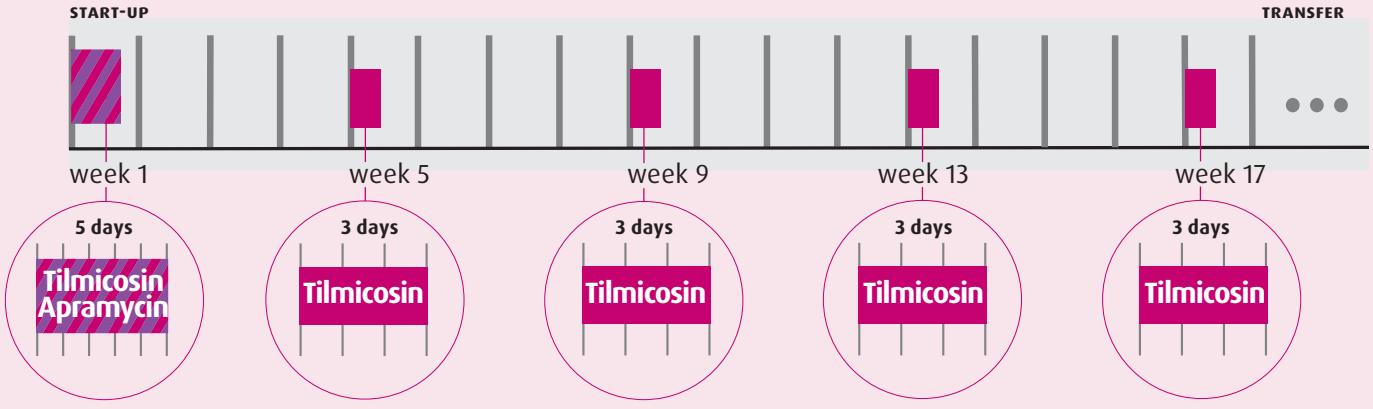


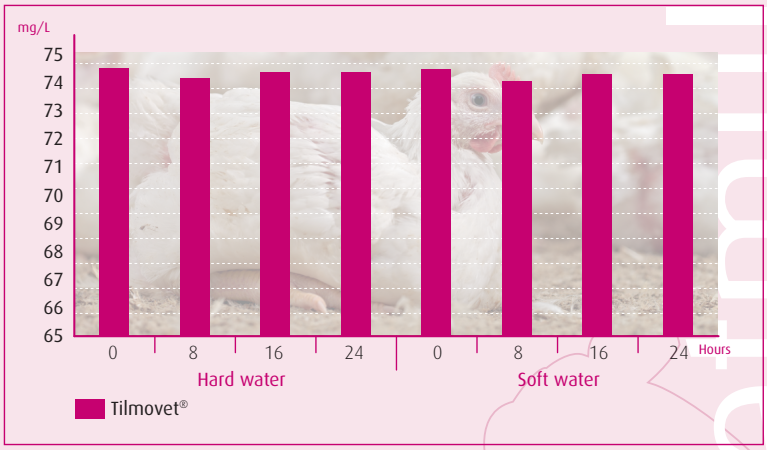
Figure 4. Treatment program pullets

Tilmovet® 250 mg tilmicosin/ ml concentrate for oral solution

1. Tilmovet® 250 mg /ml is stable in:

a. Soft and hard water
b. Water of 4°C and 20°c

"Several tilmicosin containing products on the market have suboptimal in-use stability".

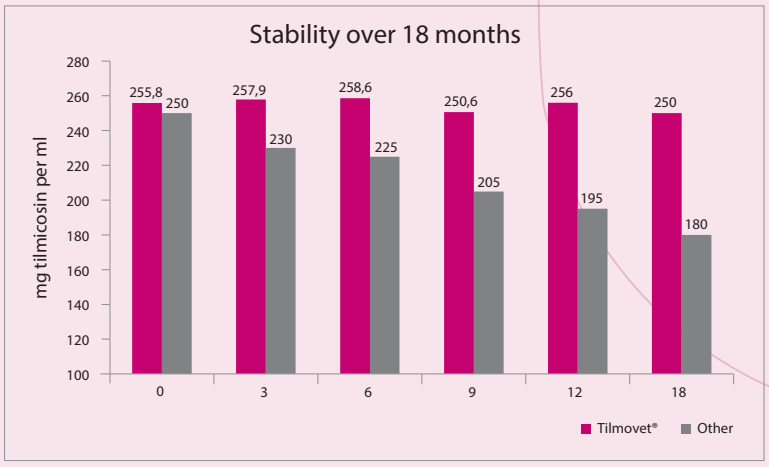


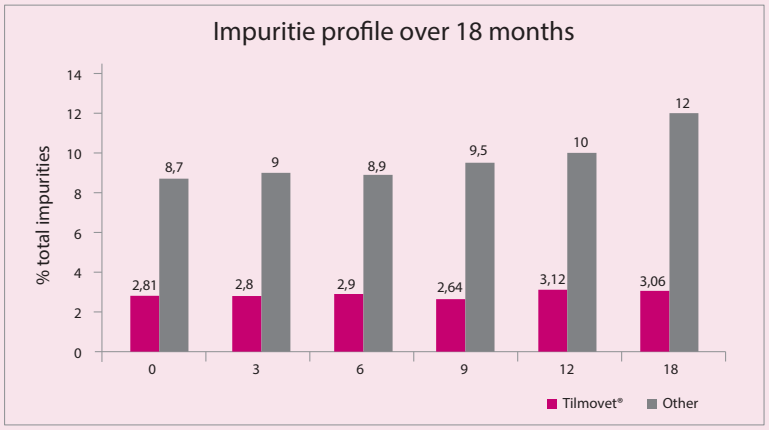
2. Tilmovet® has AND maintains a low impurity profile

"Impurity levels are especially important for tilmicosin containing veterinary products. These impurities are potentially toxic for macrophages."

3. Tilmovet® 250 mg/ml is stable during storage:

"Several tilmicosin containing products on the market lose their activity and have increasing levels of impurities during storage":





Contraindications

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

Special warnings (for each target species)

Must be diluted in drinking water or milk replacer before administration. Protect from light after reconstitution. For oral use only. Tilmicosin should not be administered by injection to pigs. The product contains disodium edetate.

Special precautions for use in animals

Pigs, broilers and turkeys: Due to the administration route and as water consumption depends on the clinical condition of the animal, in order to ensure a correct dosage, the concentration of the product must be adjusted according to the water intake. If this is not possible, then an alternative medication may be required.

Animals with acute infections and severely reduced feed intake should be treated first with a suitable injectable product.

The medicated water should be prepared fresh every 24 hours.
The medicated milk replacer should be prepared fresh every 4 hours.

Inappropriate use of the product may increase the prevalence of bacteria resistant to tilmicosin and may decrease the effectiveness of the treatment with tilmicosin related substances. It is sound clinical practice to base the treatment on susceptibility testing.

Do not allow horses or other equines access to drinking water containing tilmicosin.

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

People with known hypersensitivity to tilmicosin should avoid contact with the product. The veterinary medicinal product may cause irritation or sensitisation by skin contact.

Avoid skin and ocular contact. Wear protective gloves and protective clothes when handling the veterinary medicinal product.

In case of contact with skin or eyes, rinse abundantly with fresh water. If irritation persists and in case of incidental ingestion, seek immediately medical advice or call a poison center (dangers linked to disturbances in cardiac conduction).

Wash hands after use.

Adverse reactions (frequency and seriousness)

None known

Use during pregnancy, lactation or lay

The safety of the product has not been established during pregnancy and lactation. Use only in accordance with risk/benefit assessment by the responsible veterinarian. Do not use for pullets and laying hens producing eggs for human consumption.

Interaction with other medicinal products and other forms of interaction

Cross resistance between tilmicosin and other macrolide antibiotics and lincosamides has been observed.

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)

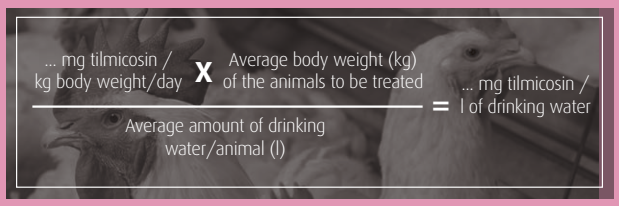
15-20 mg tilmicosin per kg BW for 3 days, i.e. 6-8 ml of the veterinary medicinal product for 100 kg BW for 3 days.

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 on 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 Dose/mg/LW		Tilmovet® 250 mg/ml dose in ml	
		15 mg/kg	20 mg/kg
Weight in kg	100	6	8
	250	15	20
	500	30	40
	1000	60	80

Turkeys Dose/mg/LW		Tilmovet® 250 mg/ml dose in ml	
		10 mg/kg	27 mg/kg
Weight in kg	100	4	11
	250	10	27
	500	20	54
	1000	40	110

If signs of disease do not significantly improve within 3 to 5 days, the diagnosis should be re-evaluated and the treatment changed. After the end of the medication period, the water supply system should be cleaned appropriately to avoid any 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 details, refer to the species-related brochure.

Packing

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 and 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 administration of the product should be avoided. Hypersensitive persons should avoid any 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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