Vetmulin®

450 mg tiamulin hydrogen fumarate/ g
Granules for use in drinking water

The proven standard

HUVEPHARMA®
We add performance to your business

Vetmulin® contains tiamulin hydrogen fumarate (thf), a semi-synthetic derivative of the naturally occurring antibiotic pleuromutilin, which is derived from the fungus *Pleurotus mutilis*. The molecule is **only used in veterinary medicine** and this is the reason the use in animal health has a low risk for human medicine (EMEA report, 1999; Alban et al., 2017).

Pharmacokinetics

After the oral administration of 25 mg tiamulin/kg BW, a Cmax of 1.7 µg/ml was measured after 4 hours (tmax). After the administration of medicated drinking water at 250 ppm (250 mg/L tiamulin hydrogen fumarate) to chickens over 48 hours, average concentrations in the serum were 0.78 µg/ml (0.45 - 1.4 µg/ml). There is a very good distribution in the tissues. Approximately 50% (45% - 52%) of the tiamulin is bound to serum proteins.
Tiamulin is rapidly metabolised in the liver (hydroxylation, de-alkalysation, hydrolysis). Excretion is through the bile and faeces (55-65%). The remainder is excreted through the urine. The elimination is biphasic: more than 99% is excreted within 24 hours, while the remaining 1% is not excreted until 6 to 8 days.

Spectrum

Tiamulin is an antibiotic mainly used for enteric and respiratory infections. The anti-bacterial effect is mainly bacteriostatic. However, for **Mycoplasma, bactericidal concentrations are easily reached** at about 16x the MIC. (Burch, 2004)

Pathogen	Number of isolates	MIC 50	MIC 90	Range	Reference
Mycoplasma gallisepticum	*20*	0,001	0,025	0.0005-0.25	Hannan et al., 1997
Mycoplasma synoviae	*28*	0,1	0,25	0.05-0.5	Hannan et al., 1997
	17	0,12	1	0.015->2	Vereecken et al., unpublished
Mycoplasma iowae	*19*	0,01	0,1	0.005-0.1	Hannan et al., 1997
Ornitobacterium rhinotracheales	*35*	0,25	0,5	0.12->0.5	Vereecken et al., 2011
	45	0,12	0,25	0.12->0.25	Devries et al., 2001
Staphylococcus aureus	*9*	0,039	0,078	0.0125->0.078	Drews et al, 1975
Gallibacterium anatis	*25*	4	8	2->8	Vereecken et al., 2015
Brachyspira pilisicoli	*20*	0,125	1	0.031->2	Verlinden et al., 2011
	17	0,1	1	0.1->1	Hampson et al., 2011
Brachyspira intermedia	*25*	0,1	4	0.1->4	Hampson et al., 2011
Erysipelothrix rhusiopathiae	*214*	3,13	6,25	0.2->6.25	Yamamoto et al., 2001
Pasteurella multocida	*132*	16	32	2->32	Vera-Lizarazo et al., 2006

susceptible potentially resistant

Figure 1. MIC's of some respiratory and enteric poultry pathogens

Indications for use

Chickens

Treatment and metaphylaxis of chronic respiratory infections (CRD) and air sacculitis caused by tiamulin-susceptible strains of *Mycoplasma gallisepticum* and *Mycoplasma synoviae*.

Turkeys

Treatment and metaphylaxis of infectious sinusitis and air sacculitis caused by tiamulin-susceptible strains of *Mycoplasma gallisepticum*, *Mycoplasma synoviae* and *Mycoplasma meleagridis*.

The egg effect

Vetmulin® has a very unique feature: it ensures that concentrations in the eggs remain above the MIC90 for both *M. gallisepticum* (0.025 µg/ml) and *M. synoviae*(0.25 µg/ml) for several days, which is the reason why excellent results are achieved to control vertical transmission in breeder stocks in the field.

Note! These concentrations are still below maximum allowed residue level in Europe (MRL EU), which explains the 0 day withdrawal time in eggs.

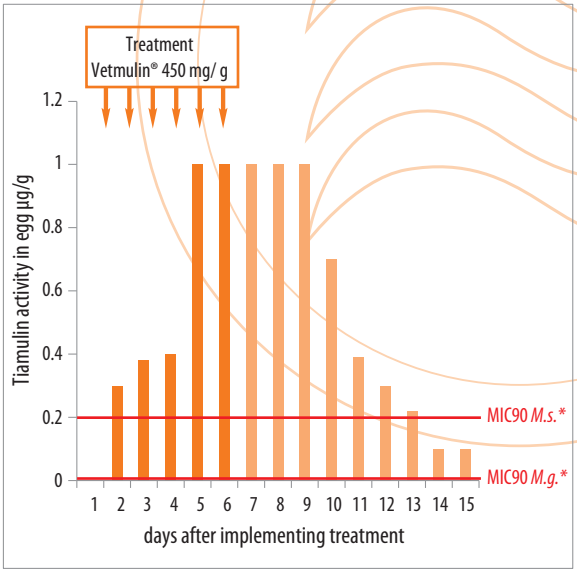


Figure 2. Concentration of tiamulin (Vetmulin®) in the egg, during and after treatment (Burch, 2004)

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

both important targets for antibiotics.

Reasons why *Mycoplasma* is still a major problem in the poultry industry.

- ***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) ensures that the biosecurity of surrounding flocks is continually challenged.
- **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 only help, in the best case scenario, 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.

Clinical signs:

Mycoplasma gallisepticum	***Mycoplasma synoviae***
Respiratory	**Respiratory**
• Sneezing • Coughing • Conjuctivitis, sinusitis	• More susceptible to viral infections and reaction on vaccination (IB/ NCD)
Poor peformance	**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

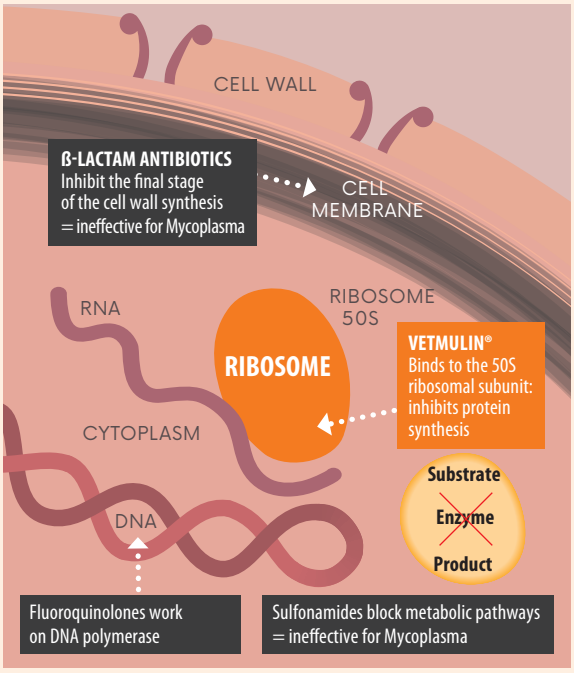
- Shows presence of DNA
- Very sensitive
- Easy transport to lab with FTA cards
- Positive / negative
  - Evaluation of Mycoplasma status: positive-negative
  - Day olds: evaluation breeder flock program

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 VETMULIN® 450 mg/g

Why Vetmulin®?



The most important considerations for a control programme are:

1. Treat for long enough 5-7 days
2. Administer daily dose as much as possible over 24 hours. NO PULSE dosing!
3. In a high risk environment: increase the treatment frequency; not the dose.

Low risk : 5-7 days:	**every 28 days**
Medium risk : 5-7 days:	**every 21 days**
High risk :5-7 days:	**every 14 days**

Dosing:

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

Two treatment groups received Vetmulin® 450mg/g in the drinking water for 5 days, starting 1 day post challenge:

- Vetmulin®: 10 mg tiamulin hf (thf) /kg bodyweight (BW) for 5 days.
- Vetmulin®: 25 mg tiamulin hf (thf) /kg bodyweight (BW) for 5 days.
- Infected Untreated Control

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

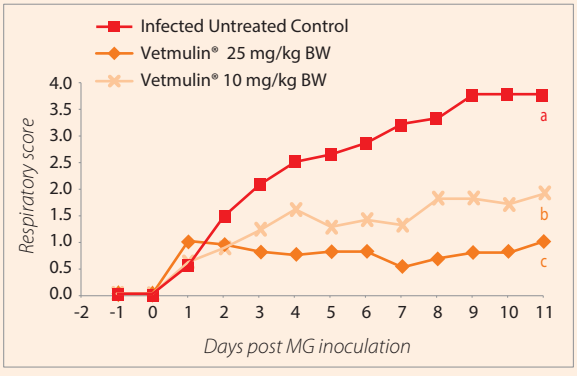
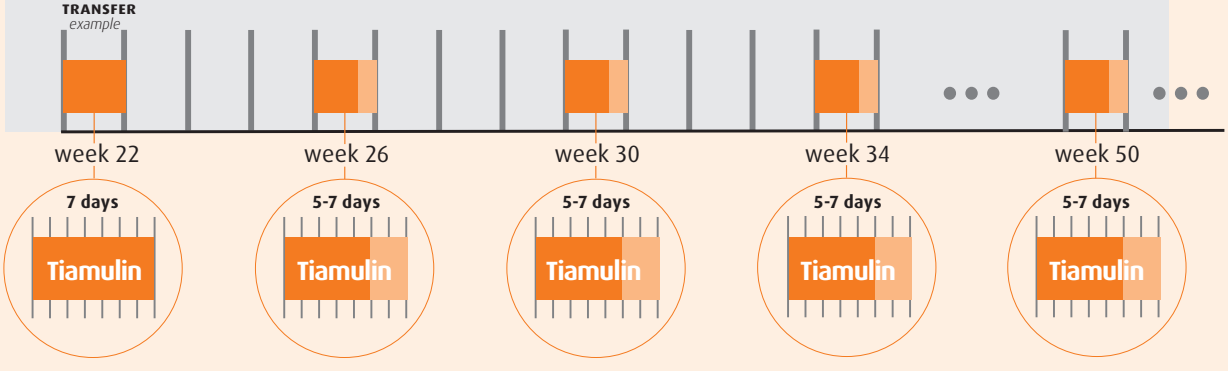


Figure 3. Mean respiratory scores (scoring system 0-4)

ref: Garmyn ***et al.***, 2017.



Vetmulin® 450mg/g: granules for use in drinking water

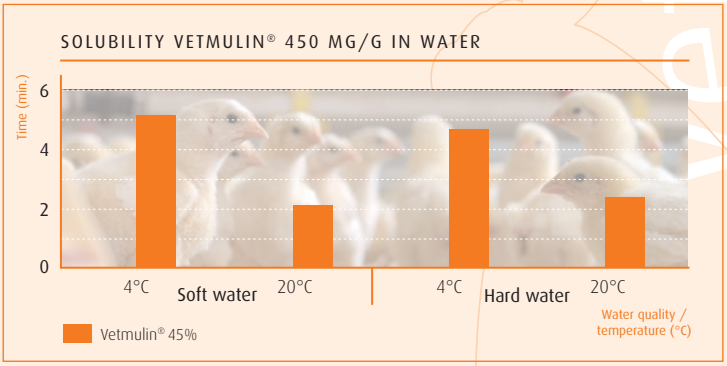
1. Vetmulin® 450mg/g is a granulated product

Vetmulin® 450mg/g granular

Other simple tiamulin mixture

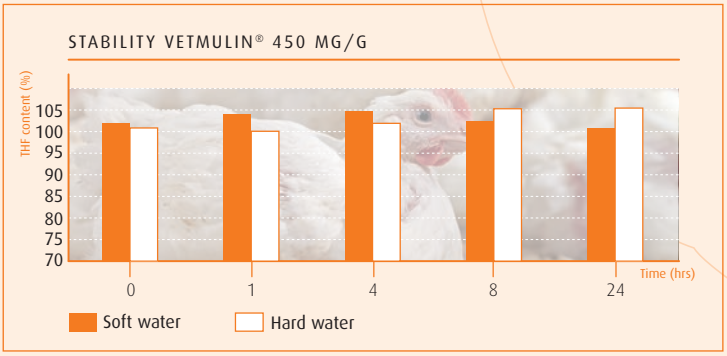
2. Vetmulin® 450mg/g is soluble in:

- Soft and hard water
- water of 4°C and 20°c



3. Vetmulin® 450 mg/g is stable in:

- Soft and hard water
- water of 4°C and 20°c



For correct dosing: Use the following formula:
Product (gram) / 1000 liter drinking water

Weight (kg) x dose (mg/kg bw)
Water intake (l) x 0.45

Example

Type of bird	Age (weeks)	Weight (kg)	Daily water intake (l)	Vetmulin® per 1000 liter drinking water (Dose: 25 mg/ kg bodyweight)	Vetmulin® per 1000 liter drinking water (Dose: 10 mg/ kg bodyweight)
Broiler breeder	23 (point of lay)	2.7	0.250	600 gram	240 gram
	30 (peak lay)	3.4	0.343	550 gram	220 gram
Layer	20 (point of lay)	1.71	0.190	500 gram	200 gram
	20 (peak lay)	1.89	0.233	450 gram	180 gram

Contra-indications

Do not use in animals with known hypersensitivity to the active ingredient or to any of the excipients. Do not use in known cases of resistance to tiamulin. Do not administer products containing ionophores such as monensin, salinomycin or narasin during or for at least 7 days before or after treatment with the product.

Special warnings (for each target species)

The uptake of medication by animals can be altered as a consequence of illness. In case of insufficient uptake of water, animals should be treated parenterally using an appropriate injectable product. Repeated use should be avoided by improving management practice and thorough cleansing and disinfection. Repeated use should be avoided by improving management practice and thorough cleansing and disinfection.

Special precautions for use in animals

Due to the likely variability (time, geographical) in the occurrence of resistance of bacteria for tiamulin, bacteriological sampling and susceptibility testing are recommended. Official, national and regional antimicrobial policies should be taken into account when the product is used. Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to tiamulin and may decrease the effectiveness of treatment with other pleuromutilins due to the potential for crossresistance. Strategic treatment should be limited to animals where tiamulin susceptible agents have been isolated in the herd or flock.

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

Direct contact with the skin, eyes and mucous membranes should be avoided by wearing overalls, impermeable rubber gloves and safety glasses when preparing or handling the product. In case of accidental eye contact, rinse the eyes thoroughly with clean running water immediately. Seek medical advice if irritation persists. When handling the product, inhalation of the dust must be avoided by wearing a disposable half-mask respirator conforming to European Standard EN 149 or a non-disposable respirator to European Standard EN 140 with a filter to EN 143. Contaminated clothing should be removed and any splashes on to the skin should be washed off immediately. Wash hands after use. Accidental ingestion should be avoided. In case of accidental ingestion, seek medical advice immediately and show the package leaflet or label to the physician. People with known hypersensitivity to tiamulin should avoid contact with the product.

Adverse reactions (frequency and seriousness)

Water intake may be depressed during the administration of tiamulin to birds. It does not appear to have any adverse effect on overall performance of the birds or efficacy of the product

Use during pregnancy, lactation or lay

The product can be administered in laying and breeding birds as no negative effects on lay, fertility or hatchability were noticed in chickens and turkeys.

Interaction with other medicinal products and other forms of interaction

Tiamulin is known to produce clinically important – often lethal – interactions with ionophore antibiotics. Therefore, animals should not receive products containing monensin, narasin, salinomycin during or at least 7 days before and after treatment with the product. Severe growth depression, ataxia, paresis or death may result.

In order to avoid interactions between tiamulin and incompatible ionophores, the feed mill supplying the feed should be notified that tiamulin will be used and that these products should not be included in the feed or contaminate the feed. The feed should be tested for the ionophores prior to use if there is any suspicion that contamination of the feed might occur. If an interaction does occur, stop tiamulin water medication immediately and replace with fresh water. Remove contaminated feed as soon as possible and replace with feed not containing the tiamulin-incompatible ionophores.

Concomitant use of tiamulin and the ionophore anticoccidial maduramicin is not recommended since it may lead to a mild to moderate growth depression in chickens. The situation is transient and recovery normally occurs within 3-5 days following withdrawal of tiamulin treatment. This does not seem to occur with the ionophores lasalocid and semduramicin.

Tiamulin may lessen the antibacterial activity of ß-lactam antibiotics whose action is dependent on bacterial growth.

Vetmulin® 450mg/g: granules for use in drinking water

Amount(s) to be administered and administration route

For oral administration through the drinking water.

Chickens:
25 mg tiamulin hydrogen fumarate per kg bodyweight per day (equivalent to 5.5g of the product per 100 kg bw per day) for 3 to 5 consecutive days.

Turkeys:
40 mg tiamulin hydrogen fumarate per kg bodyweight per day (equivalent to 8.9g of the product per 100 kg bw per day) for 3 to 5 consecutive days.

Use during lay

The product can be administered in laying and breeding birds as no negative effects on lay, fertility or hatchability were noticed in chickens and turkeys.

Interaction with other medicinal products and other forms of interaction

Tiamulin is known to produce clinically important – often lethal – interactions with ionophore antibiotics. Therefore, animals should not receive products containing monensin, narasin, salinomycin during or at least 7 days before and after treatment with the product. Severe growth depression, ataxia, paresis or death may result.

Withdrawal period

Chickens
Meat and offal: 3 days
Eggs: Zero days

Turkeys
Meat and offal: 5 days

Shelf life

- Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
- Shelf life after first opening the immediate packaging: 3 months.
- Shelf life after dilution or reconstitution according to directions: 24 hours.

Protect product as packed for sale and after first opening from frost. Do not freeze medicated water.

Special precautions for storage

- Do not refrigerate or freeze.
- Store in original container

Packaging

Block bottomed zipped 1 kg bag of polyethylene terephthalate/aluminium/low density Polyethylene.

*Use references can be obtained upon demand
*Please consult the local label and your veterinary surgeon for exact indications and posology
Use medicines responsibly
*Legal Category: POM-V

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

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