HUVEPHARMA®

Vetmulin®

450 MG/G GRANULES FOR USE IN DRINKING WATER

Indications for use

Pigs

Vetmulin® granules for use in drinking water are indicated for the treatment and control of enzootic pneumonia caused by ***Mycoplasma hyopneumoniae*** and when diseases linked to ***Brachyspira spp.*** sensitive to tiamulin are present at herd level.

Origin of the molecule

Vetmulin® 450 mg/g granules for use in drinking water contain tiamulin hydrogen fumarate (thf), a semi-synthetic derivative of the diterpene antibiotic of the pleuromutolin family. It is completely unrelated to other existing antibiotic families and is used only in animal medicine. Vetmulin® granules for use in drinking water are registered exclusively for veterinary use and primarily for the treatment and prevention of diseases linked to *Brachyspira spp*. sensitive to tiamulin but also for the treatment of enzootic pneumonia caused by *Mycoplasma hyopneumonia*.

Structure and activity

Tiamulin, a lipophilic, weak organic base is active against pathogenic Mycoplasmas, against most Gram-positive organisms (e.g. Staphylococci and Streptococci) and Gram-negative organisms (e.g. *Lawsonia intracellularis* as referred by Poolperm, P. et al 2006). It possesses a good activity against most strains of *B. hyodysenteriae* (the cause of swine dysentery – SD) and *B. pilosicoli* (the cause of Spirochaetal Colitis – SC) as reported by (Thomson, J.R. et al 2006).

Mode of action

The antibacterial effect of tiamulin is mainly bacteriostatic, through selective inhibition of bacterial protein synthesis at the 70S ribosome, with the binding site on the large subunit, near the peptidyl transferase centre. As a result protein synthesis is stopped.
Tiamulin has no direct antibacterial activity against enterobacteriae, e.g. *Salmonella spp. & E. coli*.

Product categorization and use

Vetmulin® granules for pigs are to be used in drinking water. It is available in a 450 mg/g concentration. One gram of the veterinary medicinal product contains 364.2 mg of tiamulin active (as tiamulin hydrogen fumarate: 450 mg).

Vetmulin® is also available as medicated premix formulation and oral granules for individual treatment. They are specifically suitable for systemic use, whereas the granules for use in drinking water are ideally used in a therapeutic manner.

Pharmacokinetic and dynamics

Tiamulin, derivative of pleuromutolin, is an antibacterial for systemic use and is active against pathogenic mycoplasmas, against most Gram-positive and most Gram-negative organisms. It has bacteriostatic activity and inhibits protein synthesis.
In-vitro research has shown that resistant bacterial mutants can be created through multi-step resistance. In practice however, resistance in mycoplasmas has been rarely reported. Resistance against *B. hyodysenteriae* has been noted; however this spirochete remains very sensitive to tiamulin. Cross-resistance between tiamulin, valnemulin and tylosin has been reported.

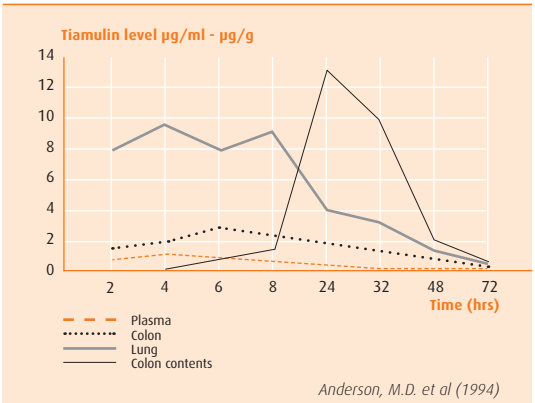
Absorption and distribution

Tiamulin hydrogen fumarate is rapidly absorbed from the gastrointestinal tract (85-90%) and appears in the blood within 30 minutes after oral administration. Following single oral doses of 10 and 25 mg/kg body weight, the C_{max} concentrations were 1.03 µg/ml and 1.82 µg/ml respectively, with a T_{max} of 2-4 hrs. There is very good distribution in the tissues with accumulation in the lungs and the colon. 30 to 50% of tiamulin is bound to serum proteins.
Tiamulin is extensively metabolized (approx. 90%) by the liver (hydroxylation, de-alkalysation, hydrolysis).

Elimination

Approximately 16 metabolites have been identified in the pig. As these possess little or no antibacterial activity, they are of no clinical importance. The major proportion of the oral dose is excreted via the bile into the gut (70-85%) and the remainder through the urine (15-30%).

MEAN TIAMULIN PLASMA AND TISSUE LEVELS

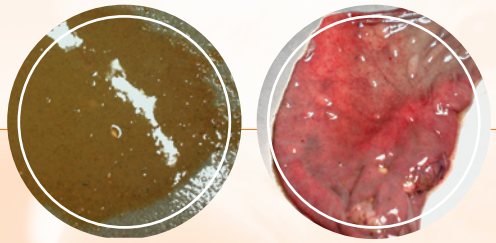


Anderson, M.D. et al (1994)

Swine dysentery

Disease

Swine dysentery (SD) is a highly fatal enteric disease characterized by bloody diarrhoea, poor productivity and death. It is caused by a large spirochaetal organism known as *Brachyspira hyodysenteriae*. Related organisms include *B. pilosicoli* and *B. murdochii*. SD occurs in most major pig producing countries and is still a major health issue in Europe and Asia. The economic losses from decreased feed efficiency have been estimated at four times the cost of medication.



PICTURES: COURTESY OF P. VYT, MEDIC LAB, AALST, BELGIUM

Transmission

SD is most common in 7-16 week old pigs but may affect older animals up to 6 months of age. Adult pigs are occasionally affected but suckling piglets rarely. The usual source of infection is through the import of pigs and happens more specifically by ingestion and transmission between pigs via faecal/oral route. Overcrowding and the build-up of faecal waste in pens contribute to an increased incidence of SD.

Symptoms

Morbidity in a group of pigs can range from 10-75% and if the animals are not treated, the case mortality rate can be as high as 50%. It is equally important however for its effect on reducing production efficiency.

Clinically only a few pigs are affected at first within a group but over a few days to two weeks it spreads to involve the majority of the group. Affected pigs are slightly depressed, show a reduced appetite and moderate fever. The faeces are only partially formed, light grey to black in color and foul smelling. Mucus, flecks of blood and epithelial casts may be seen. Blood will occur in the faeces 2-3 days after the initial onset of diarrhoea. There is a marked and rapid loss of body condition, eyes appear sunken, flanks appear hollow and the ribs and backbones appear prominent.

Animals will also have a reduced appetite but will continue to drink, possibly in subnormal amounts. Acute deaths can occur in market age pigs and adult herds when SD has been introduced for the first time. The chronic form of SD with persistent diarrhoea and failure to grow occurs with irreversible colonic lesions which at post-mortem can be found in the large intestine (colon and caecum).

Tiamulin vs swine dysentery

Several of the agents previously used against SD have been banned for public health reasons or have lost much of their efficacy through resistance problems. Tiamulin is now widely acknowledged throughout the world as the leading antibiotic for the successful control of SD.

McOrist, S. (2006) described successful experiences in eliminating SD from large breeder units (2,000-6,000 sows) via partial depopulation(*) and systemic use of tiamulin (6 weeks: 600 ppm + 6 weeks: 300 ppm). The cost-effective program allowed farrowing rates, pigs born alive per sow and average daily weight gain to improve and removed *B. hyodysenteriae* from the herd. Six months after the eradication process finished monitoring the clinical status, the herd remained SD negative.

	Pre-eradication	Post-eradication	Improvement
Farrowing rate	78-80	80-84	+3%
Pigs born alive per sow	9.5-10.6	10.4-11.3	+10%
Av. Daily weight gain (g)	630-730	680-760	+10%

McOrist, S. (2006)

(*) in combination with requisite expertise in management, hygiene, rodent control and bio-security.

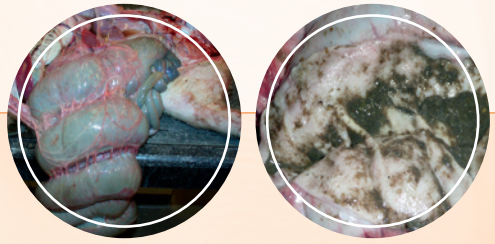
The dose rate of 8.8 mg thf - equivalent to 7.1 mg tiamulin base - per kg body weight per day for 3-5 consecutive days was found to be effective.

Another benefit of the tiamulin treatment was the removal of the *Mycoplasma hyopneumoniae* infection.

Pathology and epidemiology of related diseases

Related diseases

Related diseases are often found in the field. An example here of is described and published by Thomson, J.R. et al (2006). He found that the impact of Porcine Intestinal Spirochaetosis (PIS) is widely recognized as a common problem in growing and finishing pigs, particularly in the 20-50 kg range. It occurs in all types of housing and management systems and is caused by *B. pilosicoli*. In-vitro sensitivity shows that *B. pilosicoli* isolates are highly sensitive to tiamulin whilst resistance to tylosin and lincomycin is widespread. PIS leads to a reduced profitability resulting mainly from a decreased growth, lower feed conversion, etc. It is an ongoing problem often unnoticed since it is subclinical.
PIS typically occurs 7-14 days post-weaning or after pigs have been mixed. The same infection sources and transmission methods as SD apply.



PICTURES: COURTESY OF P. VYT, MEDIC LAB, AALST, BELGIUM

Tiamulin vs Porcine Intestinal Spirochaetosis

A controlled investigation, involving 1,835 unmedicated pigs and 1,856 medicated pigs, was made into the benefits of using tiamulin premix to combat PIS (2006, Thomson, J.R.). The trial used six consecutive batches of pigs over the course of one year on a commercial grower unit where spirochaetal colitis had been a problem. Sensitivity testing indicated that the causative organism, *B. pilosicoli*, showed good sensitivity to tiamulin (at a dose rate of 8.8 mg thf - equivalent to 7.1 mg tiamulin base - per kg body weight per day for 3-5 consecutive days).

Overall, the batches of unmedicated animals showed more evidence of diarrhoea and had significantly poorer ADG and FCR compared to tiamulin medicated pigs.
Mortality levels in both groups were similar. On top of that, the calculated benefit/cost ratio of controlling *B. pilosicoli* infection per batch of 300 pigs was calculated being 9/1.0(*).

	Non-medicated control group	Tiamulin medicated group	Benefit of tiamulin
Av. Daily Gain ADG (g)	757	880[a]	+123 g/day
Feed Conversion Rate FCR	2.03	1.77[b]	0.26 improvement
Mortality (%)	1.08	0.91	0.17%

[a] p= 0.005
[b] p< 0.001

Thomson, J.R. (2006)

(*) based on additional feed cost, overhead cost, potential loss & medication cost.

Vetmulin®

Contraindications

Do not use in case of hypersensitivity to the active substances or any of the excipients. Also do not administer products containing ionophores such as monensin, salinomycin or narasin during or at least 7 days before or after treatment with the product as growth depression or death may result. In case of doubt, test the feed for the presence of ionophores before administering.
Tiamulin may lessen the antibacterial activity of beta-lactam antibiotics, whose action is dependent of bacterial growth.

Adverse reactions

If adverse effects occur due to an interaction, the administration must be stopped immediately. In rare cases, hypersensitivity following oral administration is reported in terms of increased salivation, mild oedema, acute dermatitis and intense pruritis. These reactions are generally mild and transient but may be serious leading to apathy or death. If any of these side effects occur, stop treatment and clean animals and pens with water. Normally, affected animals recover quickly. Symptomatic treatment such as electrolyte therapy and an anti-inflammatory therapy may be useful.

Special warnings

The uptake of medication by animals can be altered as a consequence of illness. Animals having a reduced oral intake should be treated parentally using an appropriate injectable product.
Long term or repeated use should be avoided by improving management practice and thorough cleaning and disinfection.

Special precautions for use in animals

The use of Vetmulin® granules for use in drinking water should be based on susceptibility testing and take into account official and local antimicrobial policies. If there is no response to treatment within 3 days, the diagnosis should be reconsidered and treatment should be changed if necessary. Vetmulin® granules for use in drinking water can be used safely in sows during pregnancy and lactation.

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 suitable protective clothing when mixing or handling the product. In case of accidental eye contact, irrigate the eyes thoroughly with clean running water immediately. When irritation persists and in case of accidental ingestion, seek immediate medical advice or call a poison centre. Always wash hands after use.
People with known hypersensitivity to tiamulin should handle the product carefully.

Product specifications

Vetmulin® granules for use in drinking water have a white creamy tan. The product is highly soluble and is meant for ready dissolution into drinking water, allowing accurate dosing, particularly those with depressed appetite.

Stability

In accordance with the current Committee for medicinal products for veterinary use (CVMP), a number of stability test of medicated drinking water were carried out, in both soft (pH 5-7) and hard (pH 8-9) water at a concentration of 33.4 mg/l water (i.e. 15.03 µg/ml of thf) and for a period of 24 hours.
At indicated time points the solution appearance, pH, thf content and degradation products were determined.

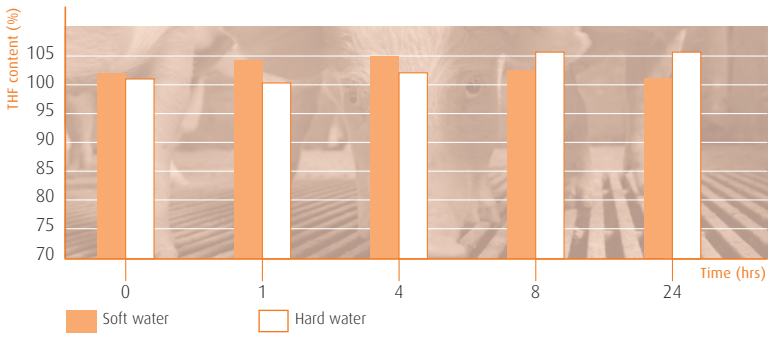
None of the test results demonstrated a decrease in the active substance content after 24 hours storage at 25°C in both types of drinking water. All values were within specification limits and no degradation products were identified.

In-use stability

In-use tests after opening of the original bags and under normal environmental conditions for 3 months, demonstrate that the characteristics of the product comply with the specification limits.

- No significant deviations in tiamulin hydrogen fumarate content and component composition values were found.
- No changes in the impurity profile were observed either.
- In terms of storage conditions, the product must be stored in the original container to protect it against direct sunlight and should not be refrigerated or frozen.

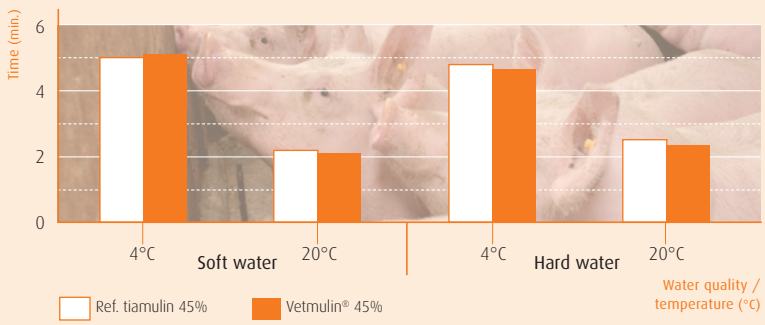
STABILITY VETMULIN® 450 MG/G



Solubility

Several comparative solubility tests have been performed in both soft (pH 5-7) and hard (pH 8-9) water at temperatures of 4°C and 20°C with a concentration of 0.556 g of tiamulin 45% granulate. Results proved that clear solutions were obtained with both products in less than 10 minutes. This means that Vetmulin® granules for use in drinking water are considered in all physiological conditions as being fully available to the animal immediately after consumption.

SOLUBILITY VETMULIN® 450 MG/G IN WATER



Amount(s) to be administered and administration route

One gram of Vetmulin® granules for use in drinking water corresponds to 450 mg of tiamulin hydrogen fumarate (thf), i.e. 364.2 mg of tiamulin base. The dose for pigs is **8.8 mg thf (equivalent to 7.1 mg tiamulin base) per kg body weight per day for 3-5 consecutive days or 15-20 mg for treating *Mycoplasma hyopneumoniae*.**

Practical administration

For the preparation of the solution, the body weight of the animals to be treated and their average water uptake should be determined as accurately as possible to avoid under or overdosing. The consumption of medicated water depends of the actual body weight, the water consumption, the clinical condition of the animals, the environment, the age and the kind of feed provided.
In order to obtain the correct dosage, the concentration has to be adjusted accordingly and by using the following formula:

$$\frac{\text{...mg thf per kg body weight and day} \times \text{Average body weight (kg)}}{\text{(Average daily water intake (l/animal) x 0.45)}} = \text{... mg Vetmulin® 450 mg/g per liter of drinking water}$$

Example: Assuming pigs weighing 50 kg, dose is 8.8 mg/kg BW and having a daily consumption of 4 liter: the farmer would need to add 245 g of Vetmulin® 450 mg/g granules for use in drinking water per 1,000 liter of drinking water.

Volume of drinking water	Vetmulin® 450 mg/g granules for use in drinking water
1,000 liter	245 g

The product can be added directly to the required volume of drinking water or a concentrated solution can be prepared to be diluted to the final concentration afterwards.

A fresh solution should be prepared each day and the use of other sources of water should be prevented. Water intake levels should be monitored at frequent intervals during medication.
The use of rusty recipients is discouraged.
The water equipment has to be cleaned adequately at the end of the treatment to avoid resistance formation by the consumption of tiamulin in subtherapeutic doses.

Withdrawal period(s)

Meat and offal

- Pigs: 5 days.

Shelf-life and Storage

- 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 on reconstitution according to directions: 24 hours.
- Store the original packaging in a dry place and protect from direct sunlight.
- Do not refrigerate or freeze.

Incompatibilities

In the absence of compatibility studies Vetmulin® should not be mixed with other medicinal products. Tiamulin is known to produce clinically important (often lethal) interactions with ionophore antibiotics.

Packaging

Vetmulin® granules for use in drinking water have a white creamy color and are packed in a block bottomed **zipped 1 kg bag**.

User warnings:
Direct contact with the skin, eyes and mucous membranes should be avoided by wearing overalls, impermeable rubber gloves and safety glasses when mixing or handling the product. In case of accidental eye contact, irrigate the eyes thoroughly with clean running water immediately. Seek medical advice if irritation persists. Dust inhalation and accidental ingestion must be avoided at all times. Seek medical advice immediately and show the package leaflet or label to the physician. Contaminated clothing should be removed and splashes onto the skin should be washed off immediately. Wash hands after use. People with known hypersensitivity to tiamulin should handle the product carefully. Any unused product or waste material should be disposed of in accordance with national requirements.

* *Used references can be requested on demand.*
* *Vetmulin® granules for use in drinking water brochure is following the authorized EU SPC (available at request).*
** *Indications listed above are not necessarily authorized in all countries. Please consult the local label for exact indications and posology.*

References:
- **McOrist, S. et al (2006)** Eradication of swine dysentery on large scale breeder farms by partial depopulation/medication. Proc. 19th IPVS Congress, Copenhagen, Denmark. Vol 1 p 319.
- **Poolperm, P. et al (2006)** Treatment comparison between tiamulin and tylosin against mixed enteric infection with PRRS co-infection in Thailand. Proc. 19th IPVS Congress, Copenhagen, Denmark. Vol 2 p 347.
- **Thomson, J.R. et al (2006)** A cost benefit study on the control of porcine colonic spirochaetosis in a commercial grower unit. Proc. 19th IPVS Congress, Copenhagen, Denmark. Vol 2 p 350.

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