HUVEPHARMA®

Vetmulin®

100 G/KG MEDICATED PREMIX

Origin of the molecule

Vetmulin® Medicated Premix contains tiamulin hydrogen fumarate (thf), a semi-synthetic derivative of the diterpene antibiotic of the pleuromutilin family. It is completely unrelated to other existing antibiotic families. Vetmulin® is registered exclusively for veterinary use.

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). Also activity against *B. pilosicoli* (the cause of spirochaetal colitis – SC) has been reported (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, causing an inhibition of the peptidyl-transferase. As a result protein synthesis is stopped.
Tiamulin has no direct antibacterial activity against entero-bacteriae, e.g. *Salmonella spp. & E. coli.*

Product categorization and use

Vetmulin® Medicated Premix is an oral medicated feeding stuff for pigs. It is available in a concentration of 100 g tiamulin hydrogen fumarate/ kg, (corresponding to 82 g tiamulin active).

Vetmulin® is also available as soluble granules for use in drinking water and oral granules for individual treatment. They are specifically suitable for therapeutic use, whereas the medicated premix for feeding stuff is ideally incorporated in controlling and therapeutic programs.

Indications for use

Pigs

Vetmulin® Medicated Premix is indicated for

- Treatment and metaphylaxis of ***Brachyspira hyodysenteriae*** sensitive to tiamulin at herd level.
- Treatment of colitis caused by ***Brachyspira pilosicoli***.
- Treatment of ileitis caused by ***Lawsonia intracellularis.***
- Treatment of enzootic pneumonia caused by ***Mycoplasma hyopneumoniae***.

Pharmacokinetic and dynamics

Tiamulin, derivative of pleuromutilin, 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.

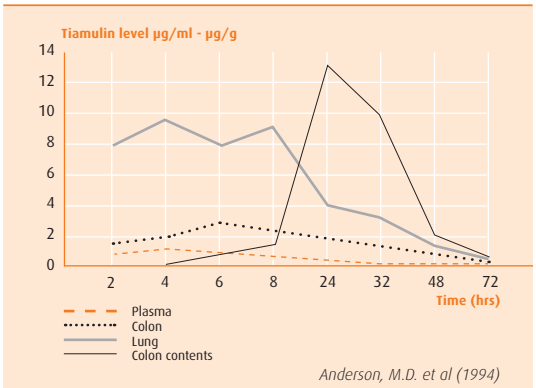
Absorption and distribution

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

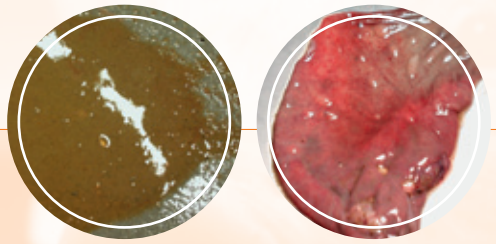


Anderson, M.D. et al (1994)

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 transportation 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).

Disease elimination

Currently the financial costs imposed by the disease (poor productivity, mortality) and a reducing number of effective antimicrobials, have motivated producers and veterinarians to use elimination strategies to overcome the disease. These strategies in most cases consist of a combination of medical treatment using Vetmulin® at the correct dose of 8.8 mg/kg BW and sanitary measures.

Whole herd depopulation and restocking
The entire herd is depopulated, the unit cleaned, disinfected and repaired and restocked with SD-free pigs. This is the simplest course of action and is advised when *B. hyodysenteriae* is not the sole organism present and when the farm staff and buildings would be unable to cope with other methods.

Whole herd treatment
This approach consists of a medical treatment prior to which manure should be removed, slurry channels emptied and some culling carried out to permit adequate cleaning and disinfection. Clinical disease should be controlled and suppressed and rodents, flies, pets should be removed from the site during the treatment period.

Partial depopulation in combination with medication of the breeding stock
This has proven to be a powerful eradication method. The infection is eliminated by medicating the breeding stock and a barrier is created between 'clean' offspring and the infected remainder of the herd.

Porcine Intestinal Spirochaetosis

Related diseases are often found in the field. An example hereof 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 *B. pilosicoli* is also associated with colitis in human and non human primates, dogs, commercial laying hens and several species of wild and zoo birds. 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.

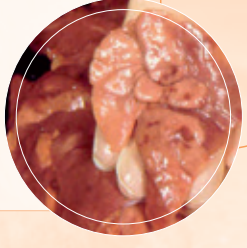
PICTURES: COURTESY OF P. VYT, MEDIC LAB, AALST, BELGIUM

Lawsonia intracellularis

Tiamulin has an excellent activity against *Lawsonia intracellularis*, the intracellular causative agent of porcine proliferative enteropathy (PPE, Ileitis) and porcine haemorrhagic enteropathy (Walter, D. *et al*, 2001). The chronic forms of proliferative enteropathy lead to clinical or sub-clinical effects on weight gain, feed conversion and fecal consistency. Clinical observations generally include diarrhoea resulting in variations in the weights of growing pigs. Acute forms with sudden death or bloody diarrhoea may be present particularly in late finishing pigs and gilts.

Mycoplasma hyopneumoniae

Mycoplasma hyopneumoniae is the primary pathogen of enzootic pneumonia. These infections are highly prevalent in almost all swine producing areas, causing significant economic losses due to an increased medication use and decreased performance of the pigs. This pathogen also plays a key role in the Porcine Respiratory Disease Complex (PRDC). Tiamulin clearly shows clinical benefits in pigs suffering from *M. hyopneumoniae* infections (Alexander *et al*, 1980).



Vetmulin®

Contra-indications

Do not use in case of resistance to tiamulin or 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 feeding.
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 of the feed must be stopped immediately. Remove the contaminated feed as soon as possible and replace with uncontaminated feed. In rare cases, hypersensitivity following oral administration is reported in terms of acute dermatitis. These reactions are generally mild and transient but may be serious. 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 feed intake should be treated parentally using an appropriate injectable product. In case of reduced feed intake, the inclusion levels in feed may need to be increased to achieve target dosage. 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® Medicated Premix should be based on susceptibility testing and take into account official and local anti-microbial policies. If there is no treatment response within 3 days, the diagnosis should be re-established. 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.
Vetmulin® Medicated Premix can be used safely in sows during pregnancy and lactation. Do not use the product in liquid feed

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.
Inhalation of the dust must be avoided by wearing a disposable half-mask (EU Standard EN149) or a non-disposable respirator (EU Standard EN140). This warning is particularly relevant to on-farm mixing, where the risk of exposure to dust is likely to be enhanced.
People with known hypersensitivity to tiamulin should handle the product carefully.

Product specifications

Vetmulin® Medicated Premix for medicated feeding stuff has a white creamy tan and is characterized by its free-flowing granular material. Vetmulin® Medicated Premix is meant for incorporation into feeding stuff only.

Stability

In accordance with the current Committee for medicinal products for veterinary use (CVMP), a number of stability tests of premix in feed were carried out, each at 30 and 100 ppm in mash feed and pelleted feed.

Results obtained in the stability study in feed at 25°C ± 2°C/ 60% HR ± 5% lead to the conclusion that the product has remained within the quality specifications after 3 months, the suggested validity period of the medicated feed, regardless of type of feed, pellet or mash.

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 dry stored below 25° C in the original container to protect it against direct sunlight.

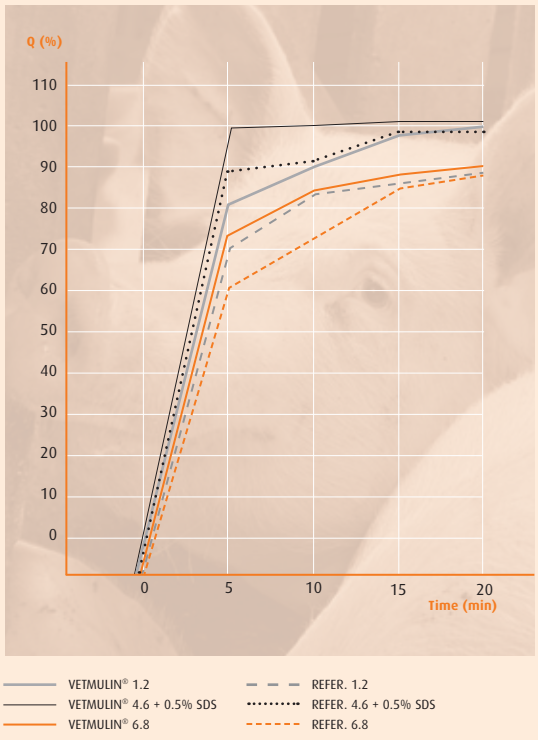
Dissolution and homogeneity

Several comparative dissolution tests using different dissolution profiles (1.2, 4.6 and 6.8 pH range) have been performed and these demonstrated that all formulations gave in all cases a mean dissolution value of 85% of tiamulin hydrogen fumarate dissolved within 15 minutes. This means that Vetmulin® Medicated Premix is considered in all physiological conditions as being fully available to the animal immediately after consumption.

Different homogeneity studies have been performed to verify the homogeneity of Vetmulin® Medicated Premix in both mash and pellet feed after manufacturing (each at different levels of production).

All samples showed standard deviations well below the legal requirements confirming the homogeneity of the used medicated premixes.

COMPARATIVE DISSOLUTION TEST OF VETMULIN® MEDICATED PREMIX WITH COMPETING REFERENCE THF FORMULATIONS



Amount(s) to be administered and administration route

One kg of Vetmulin® Medicated Premix corresponds to 100 g tiamulin hydrogen fumarate (thf), i.e. 82 g tiamulin base.

Dosage

Pigs:

- Treatment of Swine Dysentery and Porcine Colonic Spirochaetosis (colitis): 5-10 mg tiamulin thf / kg BW for 7-10 days.
- Metaphylaxis of Swine Dysentery: 2 mg tiamulin thf/ kg BW for 2-4 weeks.
- Treatment of Porcine Proliferative Enteropathy (ileitis) caused by *L. intracellularis:* 7.5 mg tiamulin thf/kg BW for 10-14 days.
- Treatment of Enzootic Pneumonia caused by *M. hyopneumoniae*: 5-10 mg tiamulin thf/kg BW for 7-10 days.

Vetmulin® Medicated Premix is also registered for chickens, turkeys and rabbits.

Practical administration

For the preparation of the medicated feed, the body weight of the animals to be treated and their average feed consumption should be taken into account. This consumption depends of age, state of health, breed and husbandry system.

In order to calculate the exact amount of premix to be added to the feed, use the following formula to achieve the target dose:

$$\frac{\text{Dose (mg/kg body weight)} \times \text{Average body weight (kg)}}{\text{Average feed intake (kg)} \times \text{Premix strength (g/kg)}} = \text{Kg premix/ton of feed}$$

Example: Assuming a pig weighing 50 kg, dose is 8.0 mg/kg BW and having a daily consumption of 2 kg of feed we need to mix:

Vetmulin® Medicated Premix
100 g/kg
2.0 kg/ton of feed

Medicated feed may be pelleted using a pre-conditioning step at a temperature not exceeding 75°C*.
To ensure correct dosing, the body weight should be determined as accurately as possible to avoid under dosing.

* 5 minutes

Withdrawal period(s)

Meat and offal

Pigs:

- Metaphylaxis (at 2.0mg/kg BW): 1 day.
- Treatment (at 5-10mg/kg BW): 6 days.

Shelf-life and storage

- Shelf-life of the medicated premix as packaged for sale: 2 years.
- Shelf-life after incorporation into meal or pelleted feed: 3 months. (if stored below 25°C).
- Shelf-life after first opening the immediate packaging: 3 months.
- Store the original packaging in a dry place and protect from direct sunlight.

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® 100 g/kg Medicated Premix for medicated feeding stuff has a white creamy tan of free-flowing granular material. The product is packed in **5 and 20 kg bags**. The 100 g/kg formulation is also available in a **1 kg bag**.
Check with your local Huvepharma® representative which pack sizes are available in your region as this may vary.

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 obtained on demand.*
** *Vetmulin® medicated premix 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.*

HUVEPHARMA®

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