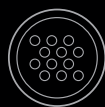
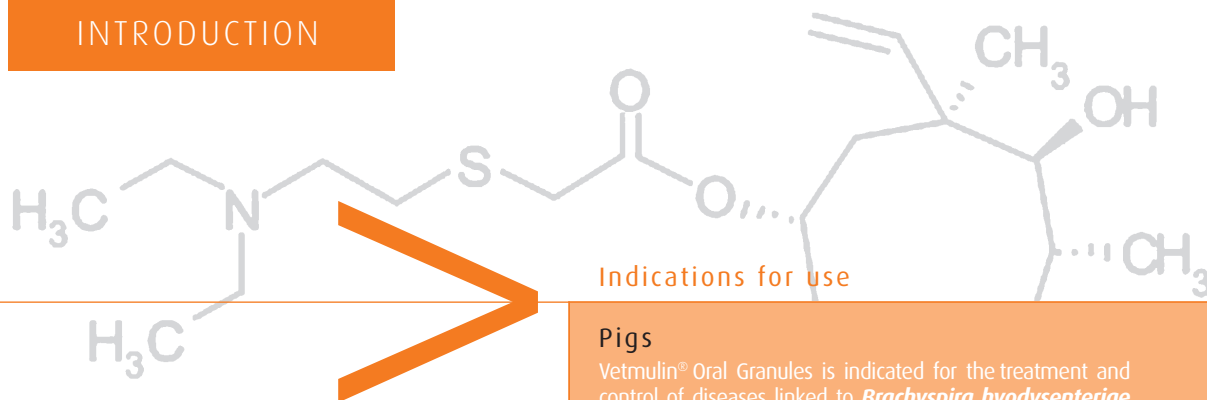




Vetmulin®

100 MG/G ORAL GRANULES FOR PIGS





Indications for use

Pigs

Vetmulin® Oral Granules is indicated for the treatment and control of diseases linked to *Brachyspira hyodysenteriae* sensitive to tiamulin, when present at herd level.

Origin of the molecule

Vetmulin® Oral Granules contain 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 and is used only in animal medicine. Vetmulin® is registered exclusively for veterinary use and primarily for the treatment and prevention of diseases linked to *Brachyspira spp.* sensitive to tiamulin.

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, 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® 100 mg/g Oral Granules is an oral therapeutic for pigs, containing 82 g of tiamulin base (as tiamulin hydrogen fumarate (thf)).

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

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 of the sensitive bacteria.

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 sensitive to tiamulin. Partial cross-resistance between tiamulin and tylosin tartrate has been reported: micro-organisms that are resistant for tiamulin are also resistant for tylosin tartrate, but not vice-versa.

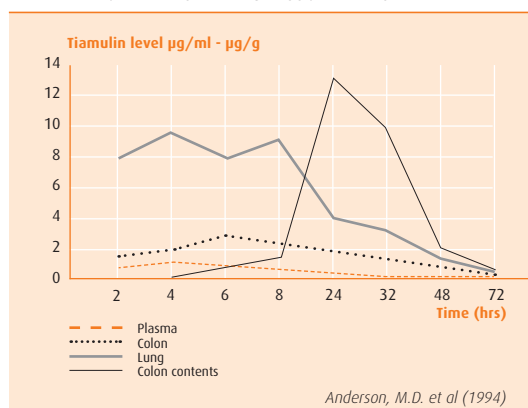
Absorption and distribution

Tiamulin hydrogen fumarate is well 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 hours. 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 hydrogen fumarate is extensively metabolized (approx. 90%) by the liver (hydroxylation, de-alkalysation and 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 is excreted through the urine (15-30%).

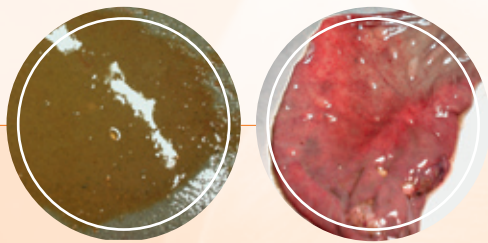
MEAN TIAMULIN PLASMA AND TISSUE LEVELS



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).

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.





Vetmulin® Oral Granules

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 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. In rare cases, hypersensitivity following oral administration is reported in terms of acute dermatitis with cutaneous erythema and intense pruritus. 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.

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® Oral Granules should be based on susceptibility testing and take into account official and local antimicrobial policies. If there is no treatment response within 3 days, the diagnosis should be re-established. Vetmulin® Oral Granules 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.

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

Product specifications

Vetmulin® Oral Granules for medicated feeding stuff has a yellowish tan and is characterized by its free-flowing granular material. Vetmulin® Oral Granules is meant for incorporation into feeding stuff only.

Practical use

The use of individual treatment is complementary to that of medicated feed. By nature, medicated feed will have to be used in all animals on a farm, or at least in all animals in a particular stable. This is very efficient when the complete herd is diseased, but is not really practical when only a limited number of animals is affected. In that case an individual treatment via the feed will have a low-stress impact which is efficient, economic and in line with the prudent use of antibiotics. In large scale operations the affected animals will be isolated in separate pens and will receive specific treatment.

Vetmulin® Oral Granules should be administered in small quantities of feed for immediate consumption by individual animals. Pigs to be treated should be separated and treated individually. For treatment of larger groups, it is recommended to use Vetmulin® medicated premix for feeding stuff.

Vetmulin® Oral Granules can be mixed thoroughly into a part of the daily feed ration and this can be administered prior to the feeding. It has to be ensured, that the calculated dose is completely taken up by the animals. Consideration must be given to pigs suffering from reduced or restricted daily feed intake. The required amount of product must be measured by suitably calibrated weighing equipment. The product should only be added to dry non-pelleted feed.

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

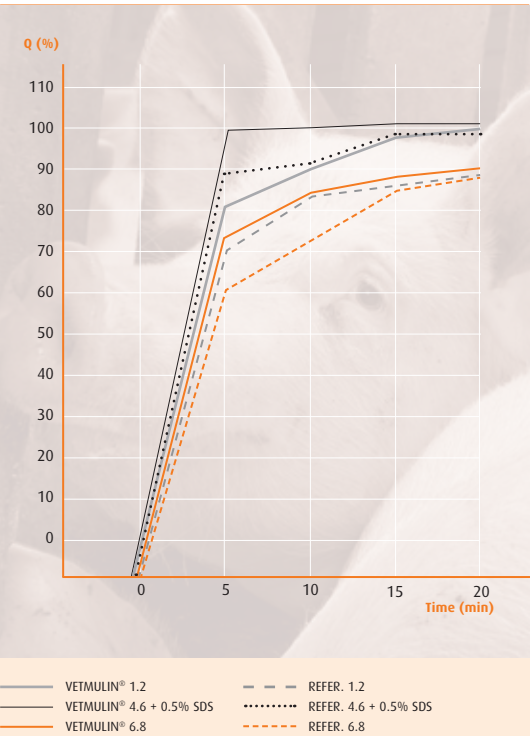
Homogeneity

Different homogeneity studies have been performed to verify the homogeneity of Vetmulin® Oral Granules in mash feed after mixing the required individual dose. All samples showed standard deviations well below the legal requirements confirming the homogeneity of the used medicated premixes.

Dissolution

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

COMPARATIVE DISSOLUTION TEST
WITH COMPETING REFERENCE THF FORMULATIONS



Amount(s) to be administered and administration route

One kg of Vetmulin® Oral Granules corresponds to 100 g of tiamulin hydrogen fumarate (thf), i.e. 82 g 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 7-10 consecutive days. Calculation of the correct dose is required.

Practical administration

The product should be administered in small quantities of feed for immediate consumption by individual animals. Pigs to be treated should be separated and treated individually. For treatment of larger groups, it is recommended to use Vetmulin® medicated premix for feeding stuff.

Make sure to determine the body weight as accurately as possible to ensure correct dosage and avoid underdosing. In case of an altered feed intake (weight class, age, environment) adjust the incorporation in order to guarantee an intake of 8.8 mg thf per kg per day.

The use of a pre-mixture is recommended to achieve a homogeneous intake. The required amount of product can first be mixed with 10% of the intended volume of feed. Mix this pre-mixture homogeneously with the feed. This must be prepared daily just before administration to the animals.

Alternatively, the product can be mixed thoroughly into a part of the daily feed ration and this can be administered prior to the feeding. It has to be ensured, that the calculated dose is completely taken up by the animals. The product should only be added to dry non-pelleted feed.

Example :

Assuming a pig weighing 50 kg, dose is 8.8 mg/kg BW, we need to administer 4.4g of the veterinary medicinal product per animal.

Withdrawal period(s)

Meat and offal

- Pigs: 7 days.

Shelf-life and storage

- Shelf-life of the medicated premix as packaged for sale: 24 months.
- Shelf-life after first opening the immediate packaging: 3 months.
- Feed to which the product has been added should be replaced if not consumed within 24 hours.
- Store in a dry place, below 25 °C, in the original container and protected from 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 mg/g Oral Granules for medicated feeding stuff has a yellowish tan and consist of free-flowing granular material. The product is packed in **250 g** and **1 kg bags**. 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 requested on demand.

* Vetmulin® Oral Granules 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:

- 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.
- Poolper, 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.

