PRODUCT SPECIFICATIONS

Product specifications

Vetmulin® Solution for injection for pigs is available in a 162 mg/ml concentration. Vetmulin® is also available as soluble granules and oral solution for use in drinking water, oral granules for individual treatment and as medicated premix formulation. The latter is ideal for incorporation in control and therapeutic programs, whereas the other formulations are designed to treat individual animals.
Vetmulin® Solution for injection has a pale yellow oily color. The product is ready for intramuscular administration. Single, individual treatment can be followed by tiamulin in drinking water or feed if necessary.

Stability

Several stability tests have been performed on tiamulin, being the active ingredient of Vetmulin® Solution for injection. During both the accelerated and long-term stability tests, Vetmulin® met the specifications throughout the whole period and data revealed no significant deviation in content values. Results obtained for other test characteristics remained within the acceptable limits.

DENSITY OILY SOLUTION VETMULIN® SOLUTION FOR INJECTION

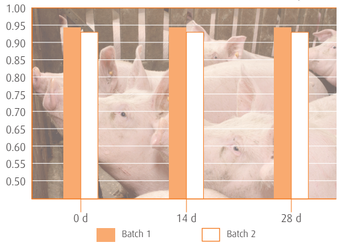
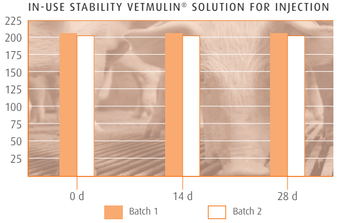


Photo-stability tests demonstrated that tiamulin content varies insignificantly and remains within the specifications when the product is directly exposed to light or when stored in plastic or metallic bottles. No degradation products have been detected under any of the experimental conditions.

IN-USE STABILITY VETMULIN® SOLUTION FOR INJECTION



In-use stability

In-use tests according to the "Note for guidance on in-use stability testing of veterinary medicinal products" (test points 0, 14 & 28 days) demonstrate that the characteristics of Vetmulin® Solution for injection comply with the specification limits.

- No significant deviations in tiamulin hydrogen fumarate (thf) 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 below 25 °C in the original container to protect it from direct sunlight and should not be refrigerated or frozen.

In-use practicability

A number of tests have been measuring the density of the oily solution, confirming full in-use practicability.

Amount(s) to be administered and administration route

One ml of Vetmulin® Solution for injection contains 200 mg of tiamulin hydrogen fumarate (thf), i.e. 162 mg of tiamulin base.

For the **treatment of clinical swine dysentery**, the dose is **8.1 mg tiamulin base** (equivalent to 1 ml per 20 kg bodyweight) to be administered in a single treatment followed by tiamulin in the water or feed.
For the **treatment of enzootic pneumonia caused by *Mycoplasma hyopneumoniae***, the dose is **12.1 mg tiamulin base** per kg bodyweight (equivalent to 1.5 ml per 20 kg bodyweight) daily for 3 consecutive days.
The **treatment of arthritis** caused by *Mycoplasma hyosynoviae* requires a dose of **12.1 mg tiamulin base** per kg bodyweight (equivalent to 1.5 ml per 20 kg bodyweight) daily for 3 consecutive days.

Depending on the severity of the disease, it may be necessary to continue treatment by orally administered tiamulin until 2 days after signs of disease have subsided.

Treatment of...	Recommended Dose			Treatment Schedule
	tiamulin base / kg BW	thf / kg BW	equivalent	
Clinical swine dysenterie	8.1 mg	10 mg	1 ml / 20 kg BW	single injection followed by tiamulin in water / feed
Enzootic pneumonia caused by *Mycoplasma hyopneumoniae*	12.1 mg	15 mg	1.5 ml / 20 kg BW	daily for 3 consecutive days
Arthritis caused by *Mycoplasma hyosynoviae*	12.1 mg	15 mg	1.5 ml / 20 kg BW	daily for 3 consecutive days

Practical administration

To ensure a correct dosage, the bodyweight should be determined as accurately as possible to avoid underdosing. The closures should not be broached more than 5 times. In order to prevent excessive broaching of the stopper, a suitable multiple dosing device should be used.
Inflammation/scarring may occur at the site of injection. For this reason, it is recommended to administer the product into the muscle of the neck.

User warnings:
Direct contact with the skin, eyes and mucous membranes should be avoided when handling the product. In case of accidental eye contact, irrigate the eyes thoroughly with clean running water immediately. Seek medical advice if irritation persists. In case of skin contact, wash immediately with running water in order to minimize absorption through the skin. Always wash hands after use. Accidental self-injection may result in severe localized reactions, particularly if injected into a joint or finger. Seek immediate medical advice and show the package leaflet or label to the physician. 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® Solution for injection 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:
(1) **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.
(2) **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.
(3) **Anderson, M.D. et al.** (1994) Tiamulin activity in certain swine tissues following oral and intramuscular administration. Proceedings of the American Association of Swine Practitioners, Chicago Illinois, USA, p. 115-118.

Withdrawal period(s)

Meat and offal

- Pigs: 21 days.

Shelf-life and storage

- Shelf-life of the veterinary medicinal product as packaged for sale: 30 months.
- Shelf-life after first opening the immediate packaging: 28 days. Discard any product remaining in the container at this time.
- Store the original packaging below 25 °C and protect from direct sunlight.
- Do not refrigerate or freeze.

Incompatibilities

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

Packaging

Vetmulin® Solution for injection has a pale yellow oily color and is presented in a 100 ml glass vial, sealed with a rubber stopper. Check with your local Huvepharma representative which pack sizes are available in your region as this may vary.

Vetmulin® Solution

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HUVEPHARMA AD • 33 JAMES BOUCHER BLVD. • 1407 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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HUVEPHARMA

Vetmulin® Solution

162 MG/ML SOLUTION FOR INJECTION

Indications for use

Pigs

Vetmulin® Solution for injection is indicated for the treatment and prevention of swine dysentery caused by ***Brachyspira hyodysenteriae*** and for the treatment of enzootic pneumonia caused by tiamulin-susceptible ***Mycoplasma hyopneumoniae*** and mycoplasmal arthritis caused by tiamulin-susceptible ***Mycoplasma hyosynoviae***.

Origin of the molecule

Vetmulin® 162 mg/ml Solution for injection contains tiamulin as base, corresponding with 200 mg/ml 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 for the treatment and prevention of diseases linked to *Brachyspira spp.* and mycoplasmata sensitive to tiamulin.

Structure and activity

Tiamulin, a lipophilic, weak organic base is active against pathogenic mycoplasmas, against most Gram-positive organisms [1] and Gram-negative organisms. 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 [2].

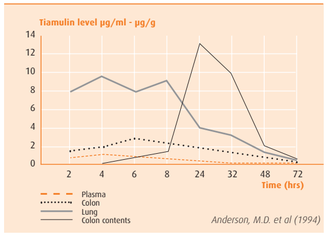
Mode of action

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*.
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; this spirochete remains sensitive to tiamulin when used in the accurate dose found after testing the sensitivity. Cross-resistance between tiamulin, valnemulin and tylosin has been reported. Bioequivalence studies of competing tiamulin formulations identified no significant differences, thus confirming full bioequivalence.

Pharmacokinetic and dynamics

Following a single intramuscular administration at a dose rate of approximately 14 mg tiamulin per kg bodyweight, mean maximum tiamulin concentration (approx. 350 ng/ml) was reached after 3 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. Studies showed that tiamulin can reach higher colon concentrations as well in the colon content as in the mucosa. Valnemulin, used as in-feed medicated premix at normal registered doses, demonstrated difficulties of reaching the MIC level.
Tiamulin is extensively metabolized (approx. 90%) by the liver (hydroxylation, de-alkalysation, and hydrolysis). The mean terminal half-life is about 12 hours.

MEAN TIAMULIN PLASMA AND TISSUE LEVELS

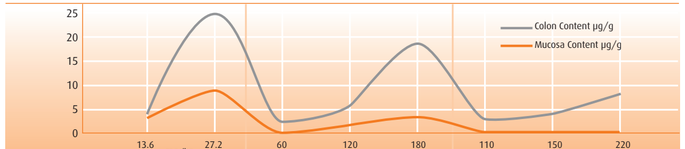


Anderson, M.D. et al (1994)

Elimination

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

TIAMULIN CONCENTRATION IN COLON



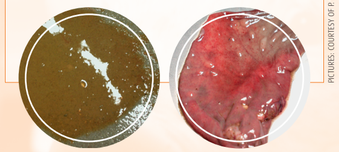
Colon Content µg/g	3.09	24.9	2.16	5.59	18.58	2.84	3.93	8.05
Mucosa Content µg/g	2.58	8.99	0	1.56	3.39	0	0	0

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*. 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%. However, it is equally important 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 thf/kg BW and sanitary measures.

Whole herd depopulation and restocking

The entire herd is depopulated, the unit cleaned, disinfected, 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.

Enzootic pneumonia

Disease

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. *M. hyopneumoniae* is considered one of the primary agents involved in the Porcine Respiratory Disease Complex (PRDC).
Combined infections with *Pasteurella multocida* and/or *Actinobacillus pleuropneumoniae* result in more severe lesions compared to the single infections. Co- or subsequent infections are commonly found in field outbreaks of enzootic pneumonia.

Recommendations for treatment and prevention

It is noteworthy that pathogen elimination in a herd is impossible, leaving room for bacterial shedding animals. However, controlled treatments during periods of risk may help to prevent an outbreak in fattening herds. Chronically infected herds may benefit from multiple treatment programs.
To treat PRDC including *M. hyopneumoniae* infections in pigs, injectable pleuromutilins can be used in individual animals and in different treatment programs. The reported acquired antimicrobial resistance of *M. hyopneumoniae* does not seem to constitute a major problem for treatment of *M. hyopneumoniae* infections to date.

Mycoplasma hyosynoviae

Disease

Arthritis caused by *Mycoplasma hyosynoviae* emerge as an important cause of lameness in pigs, especially after moving, mixing, changing feed and/or management. The upper respiratory tract of sows and finishing pigs is a predominant factor at source, as colostral immunity diminishes at the age of 6 to 8 weeks, making the animals susceptible to infection. Morbidity can be low to moderate and mortality is low.
An acute, afebrile lameness, lasting up to 10 days develops in herds of grower/finisher and/or replacement stock. The conditions can be worse after trauma or stress. Pigs will have pain in the major joints like elbows and stifles causing fluctuating swellings. Synovial fluid can contain fibrin flakes and yellow synovium. Diagnosis is made on the age of onset of clinical disease and clinical signs. Unlike polyarthritis caused by *Mycoplasma hyorhinis*, response to treatment is quite successful.

Vetmulin® Solution

Contraindications

Do not use in case of hypersensitivity to the active substances or any of the excipients. Do not use in cases of known resistance to tilmicosin. Tiamulin is known to produce clinically important (often lethal) interactions with ionophore antibiotics, including monensin, narasin, and salinomycin. Therefore, pigs should not receive products containing such compounds during or for at least seven days before or after treatment with this product. Severe growth depression or death may result. Tiamulin may lessen the antibacterial activity of beta-lactam antibiotics, whose action is dependent of bacterial growth.

Adverse reactions

In rare cases, hypersensitivity is reported in terms of acute dermatitis with cutaneous erythema and intense pruritis. These reactions are usually mild and transient but may be serious. Symptomatic treatment such as electrolyte therapy and an anti-inflammatory therapy may be useful.

Special warnings

As the product is not appropriate for use for the prevention of disease at the level of herd treatment, it should only be used for prevention of swine dysentery in individual animals with a known history of exposure to diseased animals. Long term or repeated use should be avoided by improving management practice and through cleaning and disinfection.

Special precautions for use in animals

The use of Vetmulin® Solution for injection should be based on susceptibility testing and take into account official and local antimicrobial policies. In the absence of a satisfactory response to treatment, the diagnosis should be reconsidered and treatment should be changed if necessary. Vetmulin® Solution for injection use in drinking water can be used safely during pregnancy and lactation.

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

People with known hypersensitivity to tiamulin should handle the product carefully. Care should be taken to avoid self-injection. Direct contact with the skin, eyes and mucous membranes should be avoided when handling the product. In case of accidental eye contact, irrigate the eyes thoroughly with clean running water immediately. In case of skin contact, wash immediately with running water in order to minimize absorption through the skin. Always wash hands after use. Accidental self-injection may result in severe localized reactions, particularly if injected into a joint or finger. Seek immediate medical advice and show the package leaflet or label to the physician.