HUVEPHARMA®

Vetmulin®

20 G/KG & 100 G/KG MEDICATED PREMIX

VETMULIN® 20 G/KG & 100 G/KG MEDICATED PREMIX

Target species:

Pigs

Indication:

Diseases linked to *Brachyspira spp.* sensitive to tiamulin.

Available presentations and composition:

Vetmulin® Medicated Premix 20 g as tiamulin hydrogen fumarate (thf) and 100 g/kg (both as tiamulin hydrogen fumarate (thf). Not all presentations may be marketed.

The product is presented in a **5 kg** and a **20 kg PE** in an outer paper bag. Not all pack sizes may be marketed

Contra indications:

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.

Dosage and treatment period:

Regardless of concentration, 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.

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

Withdrawal period(s):

Meat and offal

- Pigs: 7 days.

Shelf-life and storage:

Shelf-life and storage

- Shelf-life of the medicated premix as packaged for sale: 24 months.
- 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.

Vetmulin®

Vet.20&100.MPshort.0512.EN001

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HUVEPHARMA®

Vetmulin® 45 %

WATER SOLUBLE GRANULES (POULTRY)

Vetmulin® 10 %

FEED PREMIX (POULTRY)

Origin of the molecule

Vetmulin® contains tiamulin hydrogen fumarate (thf), a semi-synthetic derivate of the diterpene antibiotic of the pleuromutulin family. It is completely unrelated to other existing antibiotic families and is used only in veterinary medicine. The Vetmulin® brand name is registered in multiple countries and is exclusively for veterinary use. It's used primarily for the treatment and prevention of chronic respiratory diseases caused by *Mycoplasma spp.*

Structure and activity

Tiamulin, a lipophilic, weak organic base is active mainly against pathogenic *Mycoplasma spp.* (*Mycoplasma gallisepticum, Mycoplasma synoviae, Mycoplasma meleagridis, Mycoplasma iowae*), against most Gram-positive organisms (e.g. *Staphylococci* and *Streptococci*), *Haemophilus* spp. and obligate anaerobes. Tiamulin is, in general, not active against Gram-negative bacteria.

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.

Product categorization and use

The formulation of Vetmulin® 45 % water soluble granules is available as granules and is to be used for the preparation of an oral drinking water solution for poultry. The administration of 1 gram of product corresponds to 450mg of tiamulin active substance in the drinking water.

Vetmulin® 10% medicated feed premix is designed to be mixed homogeneously and thoroughly into the animal feed. The administration of 1 kilogram of the medicated premix Vetmulin® 10% corresponds to 100 g of tiamulin active substance per metric ton of feed.

Pharmacokinetic and dynamics

Tiamulin, a derivative of pleuromutulin, is an antibacterial for systemic use and is active against pathogenic mycoplasmas and against most Gram-positive 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 rarely been reported. Cross-resistance between tiamulin, valnemulin and tylosin has been reported.

Indications for use

Broilers, breeders, laying hens

• Treatment and prevention of mycoplasmosis caused by ***Mycoplasma gallisepticum*** and ***Mycoplasma synoviae***

Turkeys

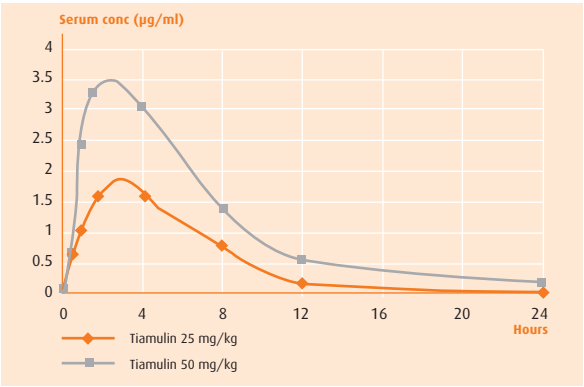
• Treatment and prevention of mycoplasmosis caused by ***Mycoplasma meleagridis***, ***Mycoplasma iowae*** and ***Mycoplasma gallispeticum***.

Absorption and Distribution

Tiamulin is rapidly absorbed from the gastrointestinal tract (85-90%) and appears in the blood within 30 minutes after oral administration. 30 to 50% of tiamulin is bound to serum proteins.
Tiamulin is extensively metabolized (approx. 90%) by the liver (by hydroxylation, de-alkalization, and hydrolysis) and excreted primarily via liver and kidneys.

An early study by Laber and Schütze (1977) looked at the serum levels of tiamulin in 7-week-old chickens after a gavaged dose of 25 mg/kg and 50 mg/kg bodyweight *(see Graph 1)*. The tiamulin concentrations in serum were determined using an agar-well microbiological assay technique with *Staphylococcus aureus* (ATCC 29067) as the test organism. The Cmax after a single gavage dose of tiamulin at 50 mg/kg bodyweight was 3.5 µg/ml and the AUC 24 hours was calculated at 32.5 µg hr/ml. Approximately linear results were achieved with 25 mg/kg bodyweight at 1.86 µg/ml and 13.72 µg hr/ml.

Graph 1
Serum levels of tiamulin following a gavaged dose of 25 and 50 mg/kg bodyweight in chickens



Tiamulin is very well absorbed in poultry and achieves high blood levels in comparison with other antibiotics.

Elimination

Tiamulin is extensively metabolized in the liver. The metabolites are eliminated within 10 days after supplementation of the product via bile and urine.

Disease

Mycoplasma infections are still considered as a major worldwide disease in modern poultry industry and are mainly caused by:

- *Mycoplasma gallisepticum*
- *Mycoplasma synoviae*

Mycoplasmas are the smallest self replicating procaryotic organisms.

Mycoplasma bacteria are vertically transmitted and establish long life infections in their host. Severity of clinical signs is strongly influenced by concurrent viral or bacterial infections and environmental factors. *Mycoplasma gallisepticum* infected flocks will suffer from respiratory symptoms, decreased egg production and performance.

In turkeys, *M. gallisepticum* causes sinusitis, pneumonia, airsacculitis and typically the paranasal swelling of the sinuses.

Mycoplasma synoviae is believed to be of growing importance as a cause of economical losses due to synovitis and respiratory disease. Some of the clinical signs in infected animals are synovitis, tracheal rales, coughing, labored breathing, and loss of general conditions.

Because of the intensified poultry industry, the disease is able to spread vertically from flock to flock through infected eggs. Infected progeny then transmit the agent horizontally either by direct bird to bird contact or by indirect contact through contaminated feed, water and equipment. Transmission can be either via droplets in the air or by sexual means. Usually, clinical signs develop 4-21 days after artificial infection in 3-4 week old broilers. The disease is typically more severe in younger birds. In laying birds, the critical age occurs around the start of egg production.

Production losses due to *Mycoplasmas*

Mycoplasma gallisepticum (MG) plays an important role as a pathogen of poultry, causing significant economic losses, particularly in the areas where the concentration of industrial farms is higher. In general, infection with *MG* will cause severe respiratory syndromes with losses an increased mortality rate and condemnation of carcasses, poor performance and increased medication costs.

Interactions with other pathogen

- Birds infected with *Mycoplasma* are more vulnerable to common respiratory field viruses or vaccines, immunosuppressive agents and poor management practices.

- Mycoplasma infection, for instance, along with *Escherichia coli* leads to complicated chronic respiratory disease (CCRD).

- Mycoplasmas also increase the sensitivity to viral infections such as Infectious Bronchitis, Infectious Laryngotracheitis and Newcastle Disease.

- In turkeys, combined infections of *Mycoplasma iowae* and other bacteria such as *Escherichia coli, Ornithobacterium rhinotracheale* or viruses like *Avian Pneumoviruses* have been described.

Tiamulin and Mycoplasma

The Vetmulin® portfolio containing tiamulin is the leading antibiotic to control and treat *M. gallisepticum (MG), M. synoviae (MS), Mycoplasma meleagridis* and *Mycoplasma iowae.*

The susceptibility of 32 isolates of *MG* and 21 isolates of *MS* isolated in Europe has been reported, using a broth dilution method to determine the minimum inhibitory concentrations (MIC):

Table 1. Comparative MICs (µg/ml) for various antibiotics against MG & MS from Europe

Antibiotic	MIC 50 (µg/ml)	MIC 90 (µg/ml)	MIC range (µg/ml)
M. gallisepticum			
Tylosin	0.016	4.0	0.008->256
Lincomycin	4.0	64	0.25->256
Tiamulin	0.008	1.0	≤0.004 - >256
Valnemulin	0.008	1.0	≤0.004 -64
M. synoviae			
Tylosin	0.031	0.062	0.008 – 0.25
Lincomycin	0.5	2.0	0.125 – 4.0
Tiamulin	0.125	0.25	≤0.004 –0.5
Valnemulin	0.008	0.008	≤0.004 – 0.16

Table 2. Comparable MIC range (µg/ml) against MG and MS

Antimicrobial	*M. gallisepticum (241)*	*M. synoviae (105)*
Tiamulin	0.0039-0.78	0.006-1.0
Tylosin	0.006-400	0.006-75
Tetracycline	0.03-0.25	0.015-5.0
Oxytetracycline	0.05-200	0.025-100
Chlortetracycline	0.05-1.56	0.05-12.5
Doxycycline	0.006-0.2	0.0125-0.78
Spectinomycin	0.39-10	0.39-6.25
Enrofloxacin	0.01-2.0	0.025-1.56
Danofloxacin	0.01-0.78	0.1-0.5
Flumequine	2.5-10	5.0-50

Tiamulin activity in other organisms

Tiamulin has shown to have activity against *Mycoplasma* species in other avian species as well as against other bacteria and Chlamydia which can cause diseases in birds. *(see table 3)*

Table 3.

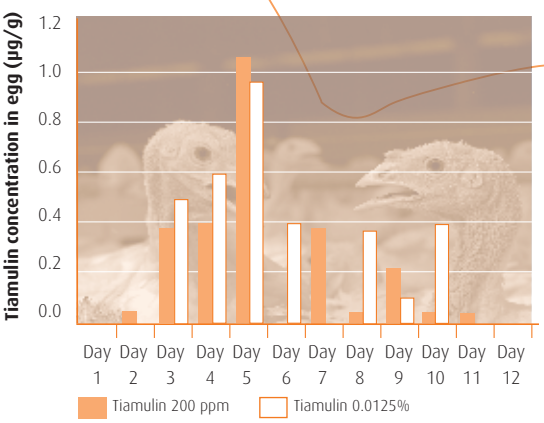
Species		*M.I.C(mcg/ml)*
Mycoplasma	*Mycoplasma anatis (ducks)*	0.1
Bacteria	*P. multocida*	0.15-8 (4 strains)
	P. gallinarum	0.5-4 (2 strains)
	Staphylococcus aureus	0.06-0.63 (38 strains)
	Clostridium perfringens	0.78
	Campylobacter jejuni	0.5-4 (8 strains)
Chlamydia	*Chlamydia Spp*	0.03-0.13 (12 strains)

Vetmulin®

Egg penetration

Tiamulin accumulates and persists in eggs following medication both in feed at 200 ppm and in water at 0.0125% (0.125 mg/ml) for several days after treatment.

By medicating the hen, the level of Mycoplasma is reduced in the hen and therefore the overall challenge of vertical infection and transmission to the eggs as well. There is also a sufficient concentration of tiamulin in the eggs to inhibit the growth of *Mycoplasma spp.*



The medication can be repeated as a recommendation to avoid vertical transmission on a monthly, two weekly or three weekly basis, depending on the *Mycoplasma* status of the flock or the risk of transmission from the proximity of infected neighbours.

Resistance

Table 4. *Mycoplasma gallisepticum, MIC ranges (µg/ml) by time period (no. of isolates)*

Antimicrobial	1975-1989 (175)	1990-2000 (66)
Tiamulin	0.0039-0.78	0.006-0.39
Tylosin	0.01-75	0.006-400
Oxytetracycline	0.12-10	0.05-200
Lincomycin	0.4-64	0.125-6.25
Enrofloxacin	0.01-0.25	0.0125-2.0

Resistance of *Mycoplasma gallisepticum* to tiamulin has rarely been described. In contrast, there is resistance development to tylosin, oxytetracycline, lincomycin and enrofloxacin and this appears to have increased in the last decade.

Mycoplasma control and treatment recommendations

Vaccination generally results in protection against vertical transmission, reduction of clinical signs and drops in egg production. However, vaccination is insufficient to prevent completely a horizontal spreading of *Mycoplasma gallisepticum*. Therefore, vaccinated birds can still be a threat and keep spreading the disease.

Biosecurity, in combination with organized control programs, remains the most common method for controlling infections caused by *Mycoplasma gallisepticum (MG) and M. synoviae (MS)*.

Medication is a very important tool to control the clinical signs and the transmission of Mycoplasma infections. To prevent antibiotic resistance in other bacteria, it is preferable to use mycoplasma selective antibiotics like the Vetmulin® portfolio (thf) over broad-spectrum antibiotics. Vetmulin® (tiamulin hydrogen fumarate) formulations should be applied in appropriate control and treatment programs which maximize the (clinical) effect and minimize the risk for resistance development.

Dose and administration

Prevention of *Mycoplasmosa*

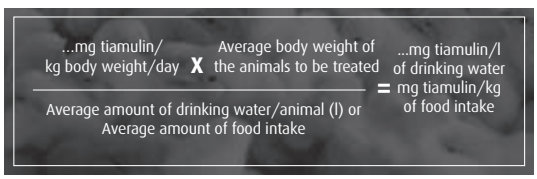
- The maximum effective dosage of tiamulin which is effective *Mycoplasma gallisepticum* is a dosage rate of 10-25 mg/kg b.w.

Treatment of *Mycoplasmosa*

- For the treatment of clinical disease in broilers, tiamulin must be used at 30 mg/kg for 3-5 days.

Practical Administration

For the preparation of medicated water and/or medicated feed, the body weight of the animals to be treated and their actual daily water/feed consumption should be taken into account. This consumption depends on the age, state of health, breed and husbandry system. To provide the required amount of active substance in mg/gram per liter of drinking water or kg of food, the following calculation should be made:



Treatment program for breeders with Vetmulin® 10 % feed premix, Vetmulin 45 % wsg and Vetmulin 80% premix (Using the Huvepharma® Dose Calculator)

Formulation of Vetmulin®	Concentration of active ingredient in %	Recommended dose in mg/kg	Weight of poultry in GRAM	Daily feed consumption in gram (poultry)	Quantity of the product in gram per ton feed
10%	10	10	335	35	957
	10	15	335	35	1435
	10	25	1260	60	5 249
	10	30	1260	60	6 299
80%	80	10	450	40	140
	80	15	450	40	210
	80	25	1560	65	749
	80	30	1560	65	899
Formulation of Vetmulin®	**Concentration of active ingredient in %**	**Recommended dose in mg/kg**	**Weight of poultry in GRAM**	**Daily water consumption in ml. (poultry)**	**Quantity of the product in gram per 1000 l of water**
45%	45	10	1060	110	214
	45	15	1060	110	321
	45	25	2195	200	609
	45	30	2195	200	731

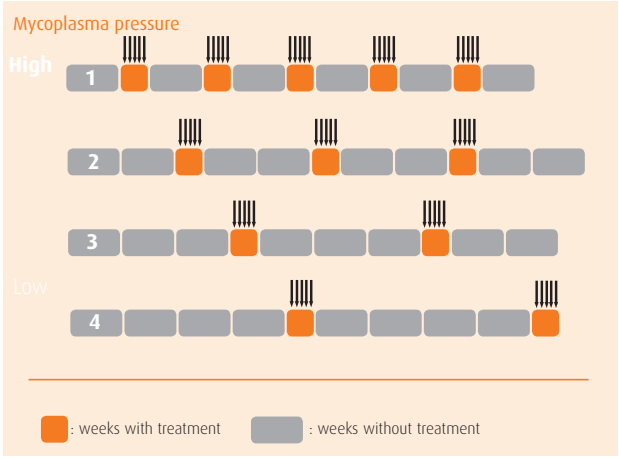
Treatment program for broilers with Vetmulin® 10 % feed premix, Vetmulin 45 % wsg and Vetmulin 80% premix (Using the Huvepharma® Dose Calculator)

Formulation of Vetmulin®	Concentration of active ingredient in %	Recommended dose in mg/kg	Weight of poultry in GRAM	Daily feed consumption in gram (poultry)	Quantity of the product in gram per ton feed
10%	10	10	340	50	680
	10	15	340	50	1020
	10	25	1400	160	2187
	10	30	1400	160	2625
80%	80	10	480	70	85
	80	15	480	70	128
	80	25	1145	140	255
	80	30	1145	140	306
Formulation of Vetmulin®	**Concentration of active ingredient in %**	**Recommended dose in mg/kg**	**Weight of poultry in GRAM**	**Daily water consumption in ml. (poultry)**	**Quantity of the product in gram per 1000 l of water**
45%	45	10	430	130	73
	45	15	430	130	110
	45	25	850	230	205
	45	30	850	230	246

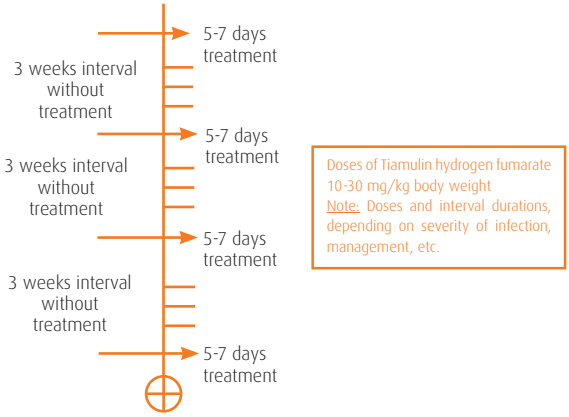
Recommended treatment schemes

I. *Mycoplasma* treatment in breeders and rearing birds

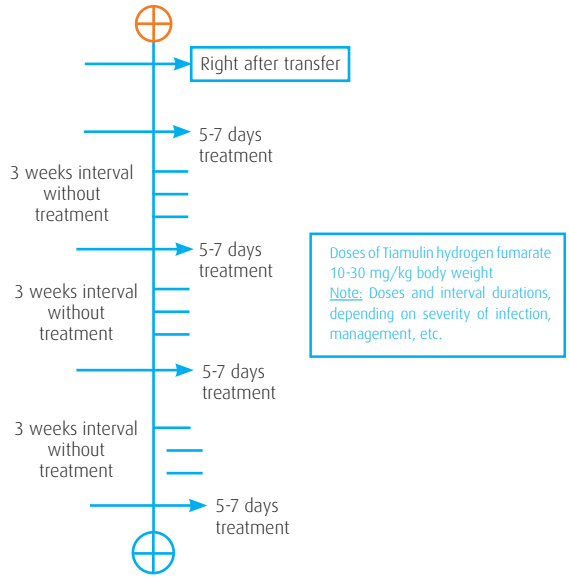
GRAPH 4. TREATMENT APPROACH



TREATMENT SCHEME FOR MYCOPLASMOSA IN REARING BIRDS

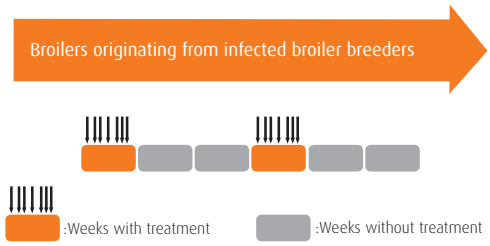


TREATMENT SCHEME FOR MYCOPLASMOSA IN PRODUCTION BIRDS



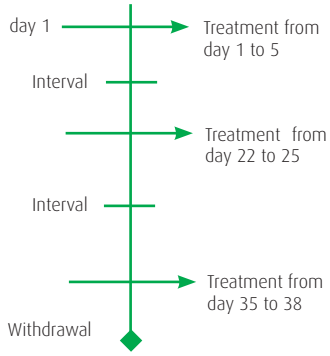
II. *Mycoplasma* treatment in broilers, birds for meat and turkeys

GRAPH 5. TREATMENT APPROACH



Because of the vertical transmission of *Mycoplasma* infection, Huvepharma® recommend treatment during the first days of life.

TREATMENT SCHEME FOR MYCOPLASMOSA IN BROILERS



Doses of Tiamulin hydrogen fumarate 10-30 mg/kg body weight
Note: Doses and interval durations, depending on severity of infection, management, etc.

Contraindications

Do not use in case of hypersensitivity to the active substances or any of the excipients. 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® in drinking water and in the feed 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.

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.

In-use stability

In-use tests after opening of the original bags and under normal environmental conditions, 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.

Withdrawal period

Vetmulin 45% wsg: please consult your local registration.
Vetmulin 10% feed premix: please consult your local registration.

Synergistic activity with tetracyclines

The good synergistic activity of tiamulin with tetracyclines, offers the veterinarian and poultry producer an effective alternative for combined treatment with tetracyclines, as an effective and economic broad-spectrum control of many mixed *Mycoplasma* and bacterial infections.

Packaging

Vetmulin® 45% water soluble granules and Vetmulin® 10% feed premix have a white creamy color.
The products are available packed in 10, 100 and 125 grams of aluminium sachets and in bags of 1, 5, 20 and 25 kg.
Check with your local Huvepharma® representative which pack sizes are available in your region as this may vary.

Shelf-life

• Vetmulin® 45 % wsg – 2 (two) years from date of manufacture.

• Vetmulin® 10% premix – Please, check your local Huvepharma® registration.

Safety

Toxicity studies have shown that tiamulin is well tolerated in poultry. Tiamulin has a relatively wide therapeutic index, with a low risk of overdose mainly due to the fact that high concentrations result in decreased water consumption and hence decreased consumption of tiamulin. The LD50 for chicken is 1090 mg/kg bodyweight and 840mg/kg bodyweight for turkeys. In a range of safety studies, tiamulin has shown to be non-mutagenic, non-carcinogenic and non-teratogenic and can therefore be regarded as a relatively low toxic risk medication.

Vetmulin®

* *Used references can be requested on demand.*
* *The Vetmulin® brochure follows the authorized EU SPC (available at request).*
* *The indications listed above are not necessarily authorized in all countries. Please consult the local SPC for exact indications and posology.*
* *Use Medicines Responsibly.*
* *Marketing Authorization Number for Vetmulin 45% WSG: VM30282/4002*
* *Marketing Authorization Number for Vetmulin 10% Premix: VM30282/4011*

Vet45.wsg&Vet10.mp.0217.EN004/Novis

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