SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Tyawalt 450 mg/g granules for use in drinking water for pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains:

Active substance:
Tiamulin hydrogen fumarate 450 mg (corresponds to 364.28 mg of tiamulin base)

Excipients:

Qualitative composition of excipients and other constituents
Lactose monohydrate

White to almost white small granules.

3. CLINICAL INFORMATION

3.1 Target species

Pigs.

3.2 Indications for use for each target species

Treatment of swine dysentery caused by *Brachyspira hyodysenteriae* susceptible to tiamulin.
Treatment of porcine colonic spirochaetosis (colitis) caused by *Brachyspira pilosicoli* susceptible to tiamulin.
Treatment of porcine proliferative enteropathy (ileitis) caused by *Lawsonia intracellularis* susceptible to tiamulin.
Treatment and metaphylaxis of enzootic pneumonia caused by *Mycoplasma hyopneumoniae*, including infections complicated by *Pasteurella multocida* susceptible to tiamulin. The presence of the disease in the group must be established before the product is used.
Treatment of pleuropneumonia caused by *Actinobacillus pleuropneumoniae* susceptible to tiamulin.

3.3 Contraindications

Do not use in animals with known hypersensitivity to the active ingredient or to any of the excipients.

Do not use in pigs that could receive products containing monensin, narasin or salinomycin during or for at least seven days before or after treatment with tiamulin. Severe growth depression or death may result.
See section 3.8 for information regarding interaction between tiamulin and ionophores.

3.4 Special warnings

Animals with reduced water intake and/or in a debilitated condition should be treated parenterally.

3.5 Special precautions for use

Special precautions for safe use in the target species:

Use of the product should be based on identification and susceptibility testing of the target pathogen(s). If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogens at farm level, or at local/regional level.
Use of the product should be in accordance with official, national and regional antimicrobial policies.
An antibiotic with a lower risk of antimicrobial resistance selection (lower AMEG category) should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.
Not for use for prophylaxis.
Inappropriate use of the veterinary medicinal product may increase the prevalence of bacteria resistant to tiamulin.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:

People with known hypersensitivity to tiamulin should avoid contact with the veterinary medicinal product.
When mixing, direct contact with the skin and mucous membranes should be avoided.
Wear safety glasses, and rubber or latex gloves when handling or mixing the product. Wash hands with soap and water after use.
If accidental contact occurs, contaminated clothing should be removed and any splashes to the skin or mucous membranes should be washed off immediately.
In case of accidental eye contact, irrigate the eyes thoroughly with clean running water immediately.
Seek medical advice if irritation persists, and show package insert or labelling to the physician.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Pigs:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Erythema or mild skin oedema

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See also the last section of the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Pregnancy and lactation:
Can be used in pigs during pregnancy and lactation.

3.8 Interaction with other medicinal products and other forms of interaction

Tiamulin has been shown to interact with ionophores such as monensin, salinomycin and narasin and may result in signs indistinguishable from an ionophore toxicosis. Animals should not receive products containing monensin, salinomycin or narasin during or at least 7 days before or after treatment with tiamulin. Severe growth depression, ataxia, paralysis or death may result.

If signs of an interaction do occur, stop both the administration of tiamulin-medicated drinking water and also the administration of ionophore-contaminated feed immediately. The feed should be removed and replaced with fresh feed not containing the anticoccidials monensin, salinomycin or narasin.

3.9 Administration routes and dosage

For use in drinking water.

Guidance for preparing product solutions:
When medicating large volumes of water, prepare a concentrated solution first and then dilute to the required final concentration. Alternatively, the concentrated solution can be used in a proportional water medicator. The solubility of the product has been confirmed at the maximal concentration of 100 g of product/L in soft and hard water and at 4°C and 20°C.

Medicated drinking water should be refreshed or replaced every 24 hours.

Make sure the animals do not have access to non-medicated water during the period when the medicated water is given.

After the end of the medication period the water supply system should be cleaned appropriately to avoid intake of sub-therapeutic amounts of the active substance.

To ensure a correct dosage, body weight should be determined as accurately as possible.

The intake of medicated water depends on the clinical condition of the animals. In order to obtain the correct dosage, the concentration of tiamulin may need to be adjusted accordingly

In order to avoid interactions between the ionophores and tiamulin, the veterinarian and farmer should check that the feed label does not state that it contains salinomycin, monensin and narasin.

The feed should be tested for the ionophores prior to use if there is any suspicion that contamination of the feed might occur.

If an interaction does occur, stop tiamulin medication immediately and replace with fresh drinking water. Remove contaminated feed as soon as possible and replace with feed not containing the tiamulin-incompatible ionophores.

Based on the recommended dose and the number and weight of animals to be treated, the exact daily concentration of the veterinary medicinal product should be calculated according to the following formula:

$$\frac{\textbf{x}\text{ mg veterinary medicinal product/ kg body weight per day} \times \text{average body weight (kg) of animals to be treated}}{\text{average daily water intake (l/animal)}} = \textbf{x}\text{ mg veterinary medicinal product per litre of drinking water}$$

- For the treatment of swine dysentery caused by *Brachyspira hyodysenteriae:* 8.8 mg tiamulin hydrogen fumarate (equivalent to 19.6 mg of product)/kg body weight administered daily in the drinking water of pigs for 3 to 5 consecutive days depending on the severity of the infection and/or the duration of the disease.
- For the treatment of porcine colonic spirochaetosis (colitis) caused by *Brachyspira pilosicoli*: 8.8 mg tiamulin hydrogen fumarate (equivalent to 19.6 mg of product)/kg body weight administered daily in the drinking water of pigs for 3 to 5 consecutive days depending on the severity of the infection and/or the duration of the disease.
- For the treatment of porcine proliferative enteropathy (ileitis) caused by *Lawsonia intracellularis*: 8.8 mg tiamulin hydrogen fumarate (equivalent

to 19.6 mg of product)/kg body weight administered daily in the drinking water of pigs for 5 consecutive days.

- For the treatment and metaphylaxis of enzootic pneumonia caused by *Mycoplasma hyopneumoniae,* including infections complicated by *Pasteurella multocida*: 20 mg tiamulin hydrogen fumarate (equivalent to 44.4 mg of product)/kg body weight administered daily for 5 consecutive days.
- For the treatment of pleuropneumonia caused by *Actinobacillus pleuropneumoniae*: 20 mg tiamulin hydrogen fumarate (equivalent to 44.4 mg of product)/kg body weight administered daily for 5 consecutive days.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

Single oral doses of 100 mg tiamulin hydrogen fumarate/kg body weight caused hyperpnoea and abdominal discomfort. At 150 mg tiamulin hydrogen fumarate/kg body weight no central nervous system effects were noted except for tranquillisation. At 55 mg tiamulin hydrogen fumarate/kg body weight given daily for 14 days, a transient salivation and slight gastric irritation occurred. Tiamulin hydrogen fumarate is considered to have an adequate therapeutic index in the pig and a minimum lethal dose has not been established.

If signs of intoxication do occur promptly remove the medicated water and replace with fresh water.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

Not applicable.

3.12 Withdrawal periods

Meat and offal: 2 days (8.8 mg tiamulin hydrogen fumarate (equivalent to 19.6 mg of product)/kg body weight).
Meat and offal: 4 days (20 mg tiamulin hydrogen fumarate (equivalent to 44.4 mg of product)/kg body weight).

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code:

QJ01XQ01

4.2 Pharmacodynamics

Tiamulin is a bacteriostatic semi-synthetic antibiotic belonging to the pleuromutilin group of antibiotics and acts at the ribosomal level to inhibit bacterial protein synthesis.

Tiamulin has shown a high level of *in vitro* activity against porcine *Mycoplasma* species as well as gram-positive anaerobes (clostridia), gram-negative anaerobes (*Brachyspira hyodysenteriae*, *Brachyspira pilosicoli),* and gram-negative aerobes (*Actinobacillus pleuropneumoniae* and *Pasteurella multocida*).

Tiamulin has been shown to act at the 70S ribosome level and the primary binding sites are on the 50S subunit. It appears to inhibit microbial protein production by producing biochemically inactive initiation complexes, which prevent elongation of the polypeptide chain.

Bactericidal concentrations can be reached but vary according to the bacterium. It can be as little as two times the MIC for *Brachyspira hyodysenteriae* and *Actinobacillus pleuropneumoniae* but as high as 50 -100 times the bacteriostatic level for *Staphylococcus aureus*. The MIC distribution for tiamulin against *Brachyspira hyodysenteriae* is bimodal, suggesting reduced susceptibility of some strains to tiamulin. Due to technical constraints the susceptibility of *Lawsonia intracellularis* is difficult to test *in vitro*.

Resistance in *Brachyspira* spp. to pleuromutilins is due to mutations at the ribosomal target site. A combination of mutations at the peptidyl transferase centre are associated with reduced susceptibility and have been characterised in *Brachyspira* spp.

4.3 Pharmacokinetics

Tiamulin hydrogen fumarate is well absorbed in the pig (over 90%) following oral administration and widely distributed through the body. Following a single oral dose of 10 mg and 25 mg tiamulin hydrogen fumarate/kg body weight the C_{max} was 1.03 µg/ml and 1.82 µg/ml in serum respectively by microbiological assay and the T_{max} was 2 hours for both. It has been shown to concentrate in the lung, polymorphonuclear leucocytes and also in liver, where it is metabolised and excreted (70-85%) in the bile, the remainder is excreted via the kidney (15-30%). Serum protein binding is approximately 30%. Tiamulin, which has not been absorbed or metabolised, passes down the intestines to the colon. Colon contents concentrations of tiamulin have been estimated at 3.41 µg/ml following administration of tiamulin hydrogen fumarate at 8.8 mg/kg body weight.

Environmental properties
A transformation product of tiamulin is very persistent in soil.
Tiamulin may be toxic to plants and algae.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after first opening the immediate packaging: 4 months.
Shelf life after dilution in water according to directions: 24 hours.

5.3 Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

After first opening, do not store above 25ºC.
Keep the original bag tightly closed after first opening.

The product after dilution in water should be stored at temperatures below 25°C.

5.4 Nature and composition of immediate packaging

Low-density polyethylene-aluminium- polyethylene terephtalate laminated bags containing 1 kg or 5 kg granules.

Not all pack sizes may be marketed.

5.5 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Medicines should not be disposed of via wastewater <or household waste>.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Krka, d.d, Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

7. MARKETING AUTHORISATION NUMBER

Vm 01656/3069

8. DATE OF FIRST AUTHORISATION

16 January 2018

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

November 2024

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database.

Gavin Hall

Approved: 08 November 2024